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ACTION OF SEX HORMONES ON EXPERIMENTAL DIABETES*

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[WITH SPECIAL PLATE]

Total pancreatectomy demonstrated the part played by the pancreas in the pathogenesis of diabetes; it also made possible the discovery of insulin and of the importance of the hypophysis and the adrenals in the course of the disease. Furthermore, basic knowledge of carbohydrate, protein, and fat metabolism in diabetes has been obtained by the use of this method. These experiments, however, were nearly always performed in dogs and cats—animals in which total pancreatectomy provokes diabetes differing in its intensity, course, and metabolic disturbances from that seen in other species, such as birds, herbivora, and man. Moreover, the influence of many modifying factors cannot be adequately studied in diabetes of so acute and severe a course as that provoked by total pancreatectomy in cats and dogs. It is therefore a sound experimental rule that in order to obtain a good knowledge of this disease it should be studied in several species and under different conditions. Certain types of experimental diabetes with a slower development and longer course lend themselves more readily to the study of the prevention and cure, either early or late, of certain forms of diabetes. A most useful example is the diabetes obtained in rats after subtotal pancreatectomy in which about 95% of the gland has been removed (Foglia, 1944). The course of this type of diabetes in the rat has been ably described by Foglia (1944), and can be divided into three stages:

In the first stage, that of *pre-diabetes* or *unapparent diabetes*, there is no hyperglycaemia or glycosuria, the body weight increases, and there are no symptoms (Table I). It usually lasts one to two months.

TABLE I

	Glycaemia after 7 Hours' Fasting	Glycosuria	Glucose-tolerance Curve	Growth
Pre-diabetes ..	Normal	No	Normal	Normal
Incipient diabetes	Normal or less than 150 mg./100 ml.	Only postprandial	High prolonged	Diminishes or ceases
Manifest diabetes	More than 150 mg./100 ml.	Present	Diabetic	None; decrease

In the second stage, that of *incipient diabetes*, there is no hyperglycaemia after seven hours of fasting, but there is postprandial glycosuria. Furthermore, the tolerance curve for glucose becomes progressively higher and more prolonged (Foglia, Orías, and Sara, 1944; Foglia, 1945). There is an increase in the intake of food with a parallel increase in spontaneous activity (Souto-Maior and Foglia, 1944). This stage lasts into the third or fourth month.

In the third stage, that of *manifest diabetes*, there is hyperglycaemia (after seven hours of fasting, more than 150 mg. per 100 ml.) and glycosuria, ketonuria, and polyuria, with loss of body weight, fatty liver, etc. Finally, there is cachexia and death. If the diabetes in an intense form lasts several months, cataracts occur (Foglia and Cramer, 1944); in the kidney there are sclerosis or hyalinosis of the glomeruli (Foglia, Mancini, and Cardeza, 1950), progressive decrease in the phosphatase of the convoluted tubules, vacuolization (glycogen) and atrophy of some cells, and sclerosis of the basal membrane (Cardeza, Mancini, and Foglia, 1949–50). The blood pressure is normal, but diabetic rats develop hypertension following experimental perinephritis or treatment with desoxycorticosterone (deoxycortone, *B.P.*), with greater frequency and more rapidly than normal rats. They also have a larger volume of interstitial fluid (Braun-Menéndez and Martínez, 1949–50). Early on, the adrenals and kidneys become enlarged, while the thymus decreases (Foglia, 1945b).

In the first and second stages the administration of glucose provokes progressively higher hyperglycaemic curves with a greater formation of muscular and hepatic glycogen in relation to the intensity of hyperglycaemia. In the third stage the storage of glycogen, in particular in the liver, is much less for the same or greater degrees of hyperglycaemia (Foglia, 1945).

The incidence of diabetes and the rapidity of its development are in relation to the amount of pancreas removed, for which reason comparative experiments must be made using many controls, and preferably all the rats should be operated upon on the same day by the same skilled operator.

With the method of subtotal pancreatectomy the following problems may be studied: (*a*) the factors which raise the proportion of rats developing diabetes and increase its severity; (*b*) those which prevent or lower the incidence of its appearance; and (*c*) attempts at curative treatment of incipient or already confirmed diabetes.

Alloxanic and pancreatic diabetes are intensified by greater food intake (Martínez, 1946; Houssay and Martínez, 1947); hyperthyroidism (Houssay and Sara, 1945; Martínez, 1945–6; Houssay, Foglia, and Martínez, 1946; Houssay, 1937, 1946, 1948); diets rich in suet or lard (Martínez, 1945–6; Houssay and Martínez, 1947, 1948); and low-protein diet (Martínez, 1946; Houssay and Martínez, 1947).

*Ciba Foundation Lecture delivered on July 3.

Alloxanic and pancreatic diabetes are attenuated by thyroidectomy (Houssay, Foglia, Prieto Díaz, and Sara, 1945; Houssay and Sara, 1945; Martínez, 1945; Houssay, Foglia, and Martínez, 1946; Houssay, 1937, 1946, 1948) and by cysteine, the thiouracils, and other substances which increase the free SH groups in the tissues (Martínez, 1946; Houssay and Martínez, 1948; Houssay, 1950). The latter and coconut oil counteract the unfavourable effect of suet or lard (Houssay and Martínez, 1947, 1948). Certain substances such as thyroid and diethylstilboestrol at first increase the incidence and severity of diabetes, but when their action is continued there is later a decrease in both the incidence and the severity of the disease.

Difference in the Sex Incidence of Diabetes

A difference in the sex incidence of diabetes is evident when subtotal pancreatectomy (95%) has been carried out in male and female rats of the same age on the same diet *ad libitum*. The frequency is much higher in males

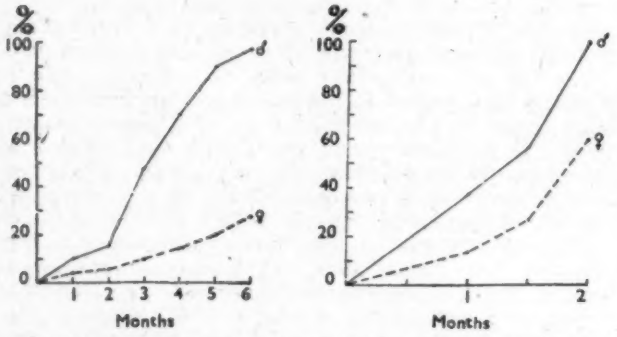

CHART 1.—Differences in the sex incidence of diabetes in 95% pancreatectomized rats. Left: with *ad libitum* feeding (93 females and 120 males). Right: paired feeding (16 pairs). (Foglia, Schuster, and Rodríguez, 1947.)

TABLE II.—*Difference in the Sex Incidence of Diabetes in Subtotally Pancreatectomized Rats Six Months After Operation (Rodríguez, 1950a)*

	No. of Rats Operated On	No. of Diabetics	Percentage
Male rats	140	125	89
Female rats ..	120	34	27

than in females (Foglia, 1945; Foglia, Schuster, and Rodríguez, 1947; Rodríguez, 1950a) (Chart 1; Table II).

The sexual difference is not due to different amounts of food. It is necessary to point this out, because in rats weighing 170 g. the males eat 27 g. and the females only 21 g. of the standard diet, and a greater food intake increases the incidence of diabetes while low food intake decreases it (Martínez, 1946; Houssay and Martínez, 1947).

In order to avoid such factors, experiments were made with paired feeding (Chart 1) and forced feeding (Chart 2). Rats of both sexes and the same weight were studied in pairs (Foglia, Schuster, and Rodríguez, 1947); the food intake of the female was weighed and the same amount given to the male the next day. In 16 paired-feeding experiments the incidence of diabetes was again higher in the males.

In forced-feeding experiments the rats received a constant quantity of food twice a day (Rodríguez, 1950a). After 40 days the incidence of diabetes in the males was

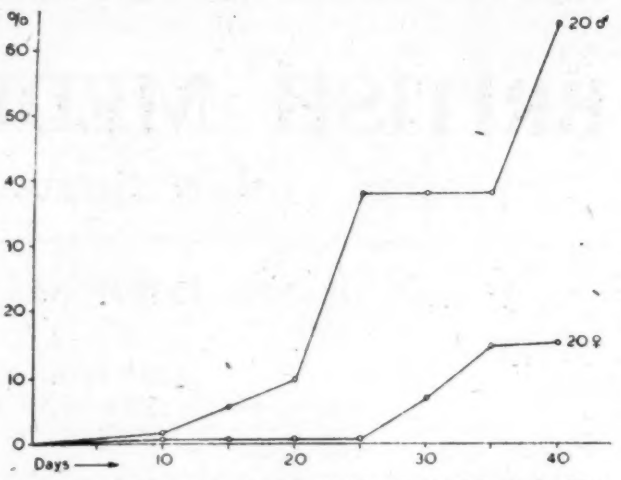

CHART 2.—Difference in the sex incidence of diabetes in 95% pancreatectomized rats forced-fed. (Rodríguez, 1950a.)

again much greater than in the females of the same weight.

These experiments with paired or forced feeding show that the difference in the sex incidence of diabetes in rats with subtotal pancreatectomy (95%) is not due to a difference in the amount of food ingested.

The sexual difference can be observed in the onset of diabetes which develops gradually after partial pancreatectomy. On the other hand, there is no sexual difference in the percentage of diabetic males and females in alloxanic diabetes (Rodríguez, 1950a) or in the severe diabetes of rats or dogs following total pancreatectomy.

Castration and Restitution

The sexual difference is due to a protective action of the ovary and a provocative action of the testicle, which is shown by experiments in castration and restitution.

The influence of castration in both sexes was shown by Foglia, Schuster, and Rodríguez (1947). In subtotal (95%) pancreatectomized rats removal of the testes diminishes the incidence of diabetes and removal of the ovaries increases it (Chart 3).

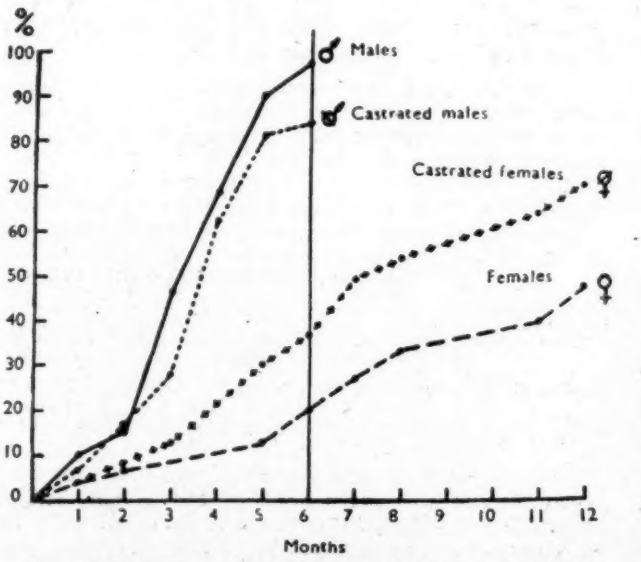

CHART 3.—Influence of castration on the incidence of diabetes after 95% pancreatectomy. Number of rats: 66 males; 32 castrated males; 30 females; 35 castrated females. (Foglia, Schuster, and Rodríguez, 1947.)

The incidence curves of male and female castrates are closer to each other than those of males and females with intact gonads. There is still, however, a considerable difference between them. These rats were castrated when their body weight was between 70 and 80 g. and had therefore been under the influence of sex hormones before pancreatectomy was performed. Dr. Foglia is now studying the effects of castration performed immediately after birth.

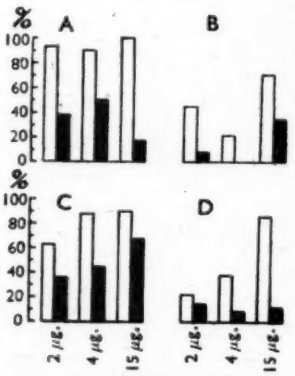

CHART 4.—Influence of injection of oestradiol benzoate on the incidence of diabetes in rats after 95% pancreatectomy. Black columns: injected. White columns: controls. A, males; B, females; C, castrated males; D, castrated females. (Foglia, Schuster, and Rodríguez, 1947.)

The restitution of the ovaries by means of a graft at the same time as subtotal pancreatectomy was performed gave considerable protection. After five months only 44% (11 out of 25) of those which had an ovarian graft had diabetes, while 85% (13 out of 15) of the non-grafted castrates were diabetic.

Protection was greater in those rats in which the graft provoked more frequent and prolonged cycles (Foglia, 1949–50). Daily subcutaneous injection of oestradiol during six months caused a marked decrease in the incidence of diabetes in castrates and controls of both sexes which had been submitted to subtotal (95%) pancreatectomy (Chart 4; Table III).

TABLE III.—*Effect of Oestradiol Benzoate Injected Daily for Six Months on the Incidence of Diabetes in Intact and Castrated Male and Female Rats after Removal of 95% of the Pancreas (Foglia, Schuster, and Rodríguez, 1947)*

Daily Dose per Rat (μg.)	Controls		Treated		Controls		Treated	
	Diabetic	%	Diabetic	%	Diabetic	%	Diabetic	%
	Intact Males				Castrated Males			
2	11/12	92	4/11	36	8/13	61	4/11	36
4	8/9	88	4/8	50	7/8	87	4/9	44
15	10/10	100	2/12	16	8/8	100	6/9	66
	Intact Females				Castrated Females			
2	6/14	43	1/12	8	2/9	22	2/12	16
4	13/63	21	—	—	19/52	37	1/13	8
15	5/7	71	2/6	33	6/7	86	1/8	12

Effects of Sex Hormones

In rats with subtotal pancreatectomy (95%) early treatment with oestrogens produced a biphasic effect: first the incidence and severity of diabetes increased, and later diabetes was attenuated or even definitely suppressed; initial intensification was seen, especially with diethylstilboestrol, and was well studied by Ingle. In forced-fed rats the appearance or intensification of glycosuria and hyperglycaemia has been observed: (*a*) in animals with partial pancreatectomy (Ingle, 1941; Rodríguez, 1950a); (*b*) temporarily in normal rats (Ingle, 1941); (*c*) in rats with alloxan diabetes (Houssay and Mazzocco, 1946; Ingle, Nezamis, and Prestrud, 1947; Ingle and Hogg, 1947); and (*d*) stilboestrol treatment provoked a fall in hyperglycaemia and glycosuria, but a high mortality, in rabbits with alloxan diabetes. Rats with alloxan diabetes fed *ad libitum* showed a fall in glycosuria and body weight, with an increase in liver glycogen, but no improvement in the diabetic state, when submitted to oestrogen treatment (Janes and Dawson, 1946). The diabetogenic effect of oestrogens has also been observed in subtotally pancreatectomized adrenalectomized rats maintained with subdiabetogenic doses of cortical extract (Ingle, 1943), and in rats submitted to these operations but not given cortical extract (Rodríguez, 1950a). The intensity of the initial diabetogenic effect increases as the amount of remaining pancreatic tissue diminishes; it is also dependent on the dose of alloxan administered and the diet.

The following results have been observed in totally pancreatectomized animals treated with oestrogens: (*a*) attenuation of diabetes in dogs (Barnes and Regan, 1933; Barnes, Regan, and Nelson, 1933) and monkeys (Nelson and Overholser, 1936); (*b*) no effect in the monkey (Collip, Selye, and Neufeld, 1937) and dogs (Young, 1941); and (*c*) increase in severity of diabetes in the ferret (Dolin, Joseph, and Gaunt, 1941) and in rats (Martínez, unpublished results).

The protective effect of steroids against diabetes following subtotal pancreatectomy was demonstrated for oestradiol by Foglia, Schuster, and Rodríguez (1947) and then for several oestrogens (Chart 5, Table IV) by Lewis, Foglia, and Rodríguez (1949–50) and for phenocycline

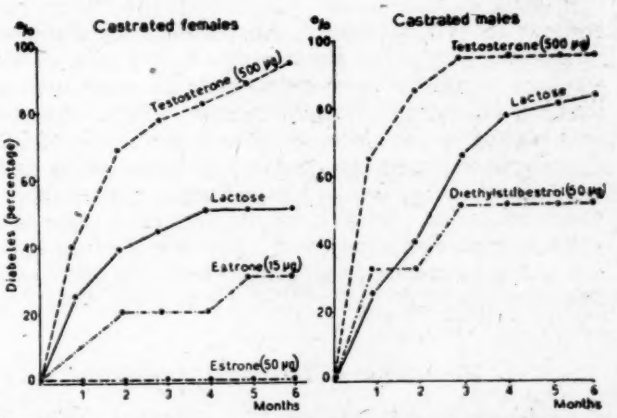

CHART 5.—Incidence of diabetes in castrated female and castrated male rats, with subtotal pancreatectomy, injected daily for six months with oestrogens and androgens (controls with lactose); daily dose per rat in micrograms. (Lewis, Foglia, and Rodríguez, 1949–50.)

TABLE IV.—*Effect of Different Substances Injected Daily for Six Months on the Incidence of Diabetes in Male and Female Castrated Rats after Removal of 95% of the Pancreas (Lewis, Foglia, and Rodríguez, 1949–50; Rodríguez, 1950a)*

	Daily Dose per Rat (μg.)	Castrated Females				Castrated Males	
		Exp. A–D		Exp. B–C			
		Diabetics	%	Diabetics	%	Diabetics	%
Lactose	25 (mg.)	12/23	52	26/35	74	16/18	89
Cholesterol	500	4/15	27	5/9	55		
Oestrone	15	3/10	30				
,,	50	0/8	0				
Diethylstilboestrol	15	3/10	30				
,,	50			1/8	12	3/6	50
Phenocycline	15	0/9	0				
,,	50	1/11	9				
Dienoestrol				1/15	6		
Ethynil-oestradiol	50			4/16	25		
,, testosterone	500			4/9	44		
Equilenine	50	6/8	75				
Progesterone	500			6/9	66		
Desoxycorticosterone	100			8/12	66		
Testosterone	50	11/15	73				
,,	500	8/8	100			13/14	92
Methyl-testosterone	500			9/11	83		
17-β-ethyl-dihydrotestosterone	500			8/11	72		

by Rodríguez (1950b). Androgens, on the contrary, caused an earlier appearance and increased the incidence and severity of diabetes.

The different substances were injected daily during six months after removal of 95% of the pancreas. The incidence of diabetes was decreased in castrated females by treatment with the following substances: oestrone, oestradiol, stilboestrol, dienoestrol, phenocycline, ethynil-oestradiol, and ethynil-testosterone. The incidence of diabetes also decreased in male castrates treated with oestrone and stilboestrol, which were the only oestrogens tested in these animals. Androgens (testosterone and methyl-testosterone) markedly increased the incidence and severity of diabetes in male and female castrates. The incidence and course of diabetes were not modified by treatment with progesterone, desoxycorticosterone, and 17-β-ethyl-dihydro-testosterone; equilenine was also inactive in the doses tested. Cholesterol produced a slight but definite decrease in the incidence of diabetes, although it has no oestrogenic effect.

To sum up, substances with oestrogenic effect decreased the incidence of diabetes in white rats following subtotal pancreatectomy. Androgens, on the contrary, increased it and other steroids had no effect.

In most animals treated with steroids the increase in body weight was less than in the controls. Many of the rats treated with oestrogens showed a loss of hair, which was considerable in some cases, while the coats of rats treated with androgens became coarse. Animals treated with oestrogens showed an increase in the weight of the hypophysis, adrenals, and uterus, and hypertrophy and hyperplasia of the islets of Langerhans in the remaining pancreatic tissue. Animals treated with testosterone had small adrenals and hypophysis. The weight of the liver and kidneys increased in animals treated with oestrogens and androgens (Lewis, Foglia, and Rodríguez, 1949–50).

Mechanism of Oestrogen Action

In order to see whether the protective effect of oestrogens was due to a difference in the amount of food ingested by the rats submitted to treatment, a series of subtotally pancreatectomized animals were forced-fed, and half of them were injected with 50 μg. of diethylstilboestrol daily. During the first month diabetes appeared in the treated animals, then the blood sugar fell to a normal level and glycosuria disappeared.

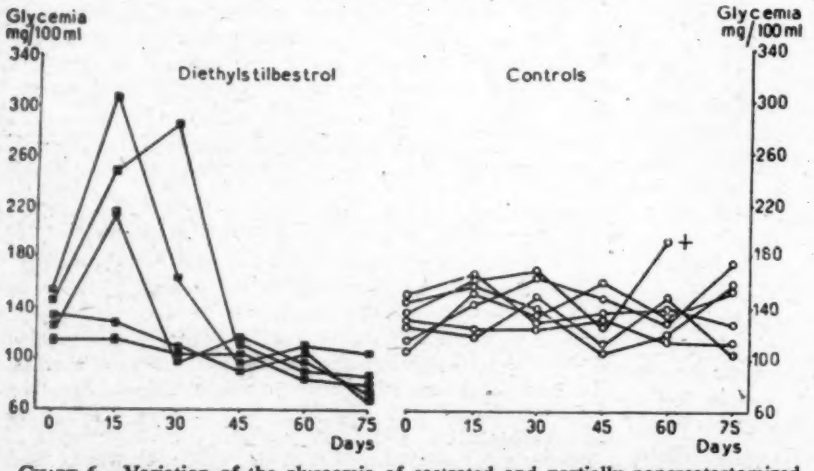

CHART 6.—Variation of the glycaemia of castrated and partially pancreatectomized female rats under forced feeding, injected with 50 μg. of diethylstilboestrol daily, and controls. (Rodríguez, 1950c.)

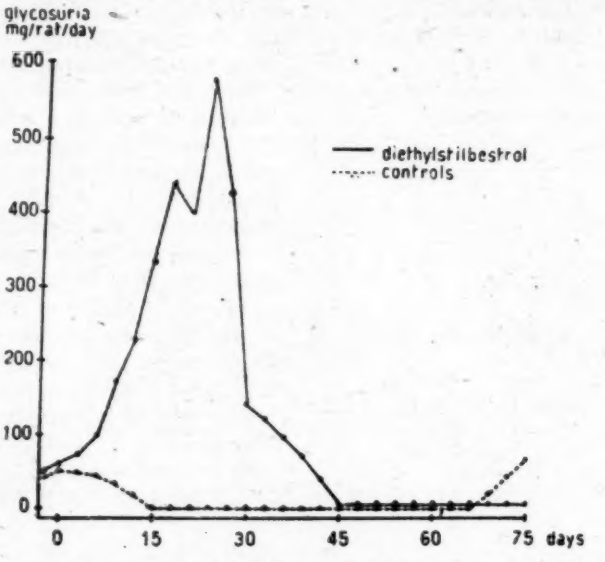

CHART 7.—Variation of the glycosuria of castrated and partially pancreatectomized female rats under forced feeding, injected with 50 μg. of diethylstilboestrol daily, and controls (average of five injected rats and seven controls). (Rodríguez, 1950c.)

In the forced-fed controls the blood sugar was at first normal, but between the 45th and 75th days after operation they all became diabetic. This experiment clearly demonstrates the initial diabetogenic and subsequent protective effect of stilboestrol (Rodríguez, 1950c).

Substances which exert a protective action against diabetes enlarge the hypophysis in most cases, but no strict correlation was observed between the increase in hypophysial weight and the protective effect (Lewis, Foglia, and Rodríguez, 1949–50).

The administration of oestrogens in rats increased the weight of the adrenals. However, the protective action could not be attributed to the adrenals, as it occurred in subtotally pancreatectomized rats already diabetic which were then adrenalectomized. Diethylstilboestrol produced first its slight diabetogenic action, and later the diabetes disappeared definitely in four out of seven rats (Chart 8). In the untreated rats adrenalectomy produced a transient decrease in the blood sugar, but after four to six weeks all the animals became diabetic again as the accessory adrenals hypertrophied; when this occurred those treated with oestradiol were protected.

The protective action of oestrogens seems to be due chiefly to the fact that they produce hypertrophy and hyperplasia of the islets of Langerhans in the pancreas. This protective action is observed in the diabetes resulting from subtotal pancreatectomy (Lewis, Foglia, and Rodríguez, 1949–50), but not in that resulting from total or almost total pancreatectomy.

Subtotal (95%) pancreatectomy is followed by a compensatory hypertrophy of the islets of Langerhans accompanied by sclerosis in some parts. This hypertrophy may be considerable after a year or more if the animal has not become diabetic. When diabetes occurs the β-cells are damaged and progressively disappear and the islets atrophy. If the diabetes

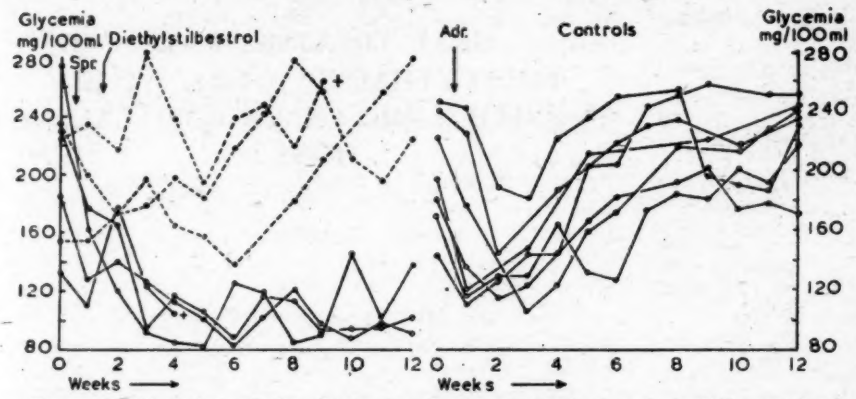

CHART 8.—Variation of the glycaemia of adrenalectomized and partially pancreatectomized male rats, under forced feeding, injected daily with 50 μg. of diethylstilboestrol, and controls. (Rodríguez, 1950a.)

occurs early there is only atrophy, but if it appears later there is first hypertrophy and then atrophy.

It has been noticed that the female rat has a greater volume of islets than the male (Tejning, 1947). After subtotal pancreatectomy the incidence of diabetes is less in females than in males, but, on the other hand, females more often present hypertrophy and hyperplasia of the islets of Langerhans (Lewis, Foglia, and Rodríguez, 1949–50; Cardeza, 1950). The stimulating factor in the female is the ovarian hormone (Table V).

TABLE V.—*Ratio Between Pancreatic Islets and Acini of Non-diabetic Castrated Female Rats, with Subtotal Pancreatectomy, Injected with Steroids During Six Months. Controls with Lactose. (Cardeza, 1950)*

Substance	No. of Animals	Weight Islets × 100 / Weight Acini
Lactose	4	1·66
Ethynil-oestradiol	2	6·94
Diethylstilboestrol	4	6·93
Oestrone	2	6·77
Dienoestrol	2	6·18
Oestradiol	3	5·42
Ethynil-testosterone	1	2·98
Progesterone	1	1·84

Oestrogens rapidly produce hypertrophy of the islets, with the formation of new islets (Del Castillo and Sammartino, 1937; Lewis, Foglia, and Rodríguez, 1949–50; Cardeza, 1950).

Confluent masses of newly formed islets can be observed which have a multilobular or ramified appearance. In certain cases the newly formed islets occupy a whole lobule of the pancreas, displacing the acini and giving the appearance of an insular adenoma (Plate, Figs. 1, 2, and 3). Hyperplasia and increase of centro-acinar cells is widespread, with the development of cells similar to β-cells (Cardeza, 1950; Rodríguez, 1950d) (Plate, Figs. 4, 5, 6, and 7). On the contrary, rats treated with androgens show early diabetes with atrophy of the islets and a marked decrease in β-cells.

Oestrogens appear to produce a direct action on the insular tissue. After intrapancreatic implantation of oestradiol, normal rats, guinea-pigs, and cats showed at first hyperplasia of the centro-acinar cells (Plate, Fig. 8), then newly formed islets containing hypertrophied cells of the β type (Plate, Fig. 9). The formation of new islet tissue was more pronounced in the zone of oestrogenic implantation.

There are two principal groups of substances which can prevent the appearance of diabetes in subtotally pancreatectomized rats — that is, oestrogens and substances which increase the free SH groups in the tissues (cysteine, thiouracils, etc.). Rodríguez and Martínez (1950) treated groups of subtotally pancreatectomized castrated female rats with oestradiol or thiouracil, or both together. Treatment with oestradiol produced two phases: an initial increase of the diabetes, followed by later protection which persisted after the treatment was discontinued. Thiouracil prevented the appearance of diabetes during treatment, but diabetes reappeared soon after treatment was discontinued in all cases.

Administration of both substances together afforded a greater degree of protection than when given separately, but on withdrawal diabetes reappeared in many animals; only 25% were protected when oestradiol alone was used.

This difference between the two substances is due to the fact that rats which received propylthiouracil were protected by its metabolic action, but it was not accompanied by hypertrophy and hyperplasia of the islets. On the other hand, rats treated with oestradiol had hypertrophy and hyperplasia of the islets of Langerhans, to which apparently the lasting protection against diabetes is due.

In some cases of alloxan diabetes a curative action of oestradiol associated with insulin has been found (Table VI). Experiments are being repeated on a larger number of animals.

TABLE VI.—*Rats with Alloxan Diabetes Treated for Six Months*

Treatment	Cured	Diabetic	Dead
Oestradiol and insulin	4	1	3
Insulin	0	3	5
Oestradiol	0	2	6

Summary and Conclusions

This group of experiments shows that after subtotal pancreatectomy diabetes appears in rats with less frequency in the female than the male. This sexual difference is due to a provocative action of the testes and androgens and a protecting influence of the ovaries and oestrogens.

The mechanism of protection is apparently chiefly due to the action of the ovaries and oestrogens in the stimulation of hypertrophy and hyperplasia of the islets of Langerhans with production of new β-cells at the expense of the centro-acinar cells.

It is difficult to say yet how far this action occurs in other species, and I would rather not discuss now whether or not it occurs in man.

The peripheral action of oestrogens upon carbohydrate metabolism is not yet well known.

The probability of preventing some forms of experimental diabetes, and even of curing a certain proportion of cases of not too severe diabetes, certainly exists.

It is evidently worth while to continue this line of investigation—using prolonged administration of those substances already studied and other new ones, either alone or combined with insulin—in order to prevent or treat other types of experimental diabetes, and eventually human diabetes.

It would be of value to discover substances which have no oestrogenic effect but cause hyperplasia of the islets and inhibit the hypophysis or adrenals. Diabetes can possibly

be controlled by other mechanisms, such as direct or indirect action on tissue metabolism.

Experimental medicine has given us most of our fundamental knowledge of diabetes, and it seems that it will continue to increase this knowledge. It also gives us hope that new methods that will prevent or even cure this disease may be discovered.

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A welfare worker of the Save the Children Fund has been working in Northern Papua since mid-May as part of the disaster relief organized in New Guinea after the volcanic explosion there early this year (*The World's Children*, September, 1951). She remarks that the average Papuan infant is smaller than the European at birth, weighing about 5 lb. Weaning begins at about 6 months old, with hard indigestible taro and rice, but an attempt is being made to teach the mothers cooking of vegetables and the preparation of porridge and other types of infant food.

ORAL TREATMENT OF POLYCYTHAEMIA VERA WITH β-NAPHTHYL-DI-2-CHLOROETHYLAMINE (R48)

BY

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AND

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Since Gilman and Philips (1946) and Rhoads (1946) published the first communications on the therapeutic action of nitrogen mustards (methyl bis-β-chloroethylamine and methyl tri-β-chloroethylamine), a number of reports on the use of these substances have appeared. On the whole there seems to be agreement that, given intravenously, nitrogen mustards can produce a distinct, but only temporary, improvement in some cases of malignant lymphogranulomatosis, lymphosarcoma, chronic leukaemia, and polycythaemia vera. As is known, the substances are cell poisons, and their inhibiting effect on bone marrow involves some risk. Thus cases of agranulocytosis have been met with after intravenous treatment with nitrogen mustard (Bjurwill, 1947; Iversen, 1951). There are also other drawbacks, such as the tendency to the formation of thrombi at the site of injection, and nausea and vomiting following the injection, while the intravenous method itself is a disadvantage, particularly as it must be carried out with due observance of various precautionary measures.

R48 by Oral Administration

Continuous work is being done with these fairly simple substances from a chemical standpoint, in order if possible to discover some which act more selectively and are less toxic. For instance, Burchenal (1948) tested two kinds of complex aliphatic nitrogen mustards, but they proved to be too toxic.

Haddow and others (1948) prepared a series of aromatic nitrogen mustards, the action of which they tested on experimentally produced tumours. Some of these substances turned out to be unsuitable for clinical use owing to their toxic effects. One of them, β-naphthyl-di-2-chloroethylamine (R48), however, seemed quite appropriate for a clinical trial. It had the added advantage that it could be administered *orally*. Clinical investigations were carried out in Oxford, and Matthews (1950) has published a preliminary report on the findings in 17 patients with various grave blood diseases. He found some improvement in five cases of Hodgkin's disease, but not more than has been observed to follow treatment with methyl-bis-β-chloroethylamine. At any rate R48 was unsuitable for the treatment of patients with localized masses of glands; *x*-ray treatment produced far better results. In two cases of reticulosarcoma and two cases of acute leukaemia there was no effect. In two out of four cases of chronic myeloid leukaemia a surprisingly good remission occurred which lasted for 11–28 weeks. These remissions could be reproduced without toxic effects. But the observation period for all these patients is still too short. The best result was observed in a patient with polycythaemia vera

in whom the remission had so far persisted for one year without any toxic effects supervening during the treatment. Matthews concludes that, on the whole, the action is basically the same as with methyl-bis-β-chloroethylamine, but it occurs more slowly and is more easily controlled.

With regard to the method of administration and dosage it is stated that the drug was given by mouth in tablets of 100 mg. The tablets are chewed, but they are tasteless. The drug is partially inactivated by light, which fact should be kept in mind. The daily dose was 300–400 mg.—at the most 600 mg. (two tablets three times a day). The original intention was to keep the disease in check with small repeated doses, but this was found to be impossible. It was therefore given for periods alternating with free intervals. No scheme for the treatment was adopted. The course of the disease in each patient was followed at first with weekly blood counts, but less frequently later on.

Like methyl-bis-β-chloroethylamine, the drug is toxic to the bone marrow, and therefore a fall in the leucocytes was observed in most cases. Apart from cases of leukaemia, this is not the object in view, nor is it desirable, but the fall sets in gradually and slowly during a period of a few weeks, and it evidently can be easily estimated. It must, however, be clearly recognized that the fall in granulocytes often continues for one to two weeks after the drug is discontinued, only to rise again spontaneously. Matthews (1950) has seen a case of granulocytopenia (550 per c.mm.) in a patient in the final stage of a reticulo-sarcoma; after stopping the drug the granulocyte count returned to normal. The thrombocyte figure also generally fell, and a case is described with a drop in the blood platelets to 55,000 per c.mm. a fortnight after the drug was discontinued. Here, again, there was a spontaneous and complete rise in the number of platelets. On the other hand, the haemoglobin percentage and the number of erythrocytes remained fairly constant.

Gastro-intestinal symptoms in the form of vomiting and diarrhoea were only exceptionally observed after R48: at most there was a little nausea in the first week. Haddow and others (1948) even met with haemorrhagic cystitis in two patients; this was possibly due to the aromatic radicle in the R48 complex, since β-naphthylamine is known in industry as a toxic substance which can cause haematuria.

Present Investigations

After having employed intravenous injections of nitrogen mustards for a year or two in various blood diseases, the attendant risks of which, as mentioned, are conspicuous in the form of nausea and vomiting after the injection and a tendency to thrombosis at the site of the injection, we felt inclined to pass on to *oral* medication with the related substance β-naphthyl-di-2-chloroethylamine, which we had heard about at second hand. On applying to Professor Haddow, of the Royal Cancer Hospital in London, we obtained some of the substance for our use under the name "preparation R48," and at first the treatment was carried out only with this preparation. Later we used a Danish preparation, "aleukon," prepared and placed at our disposal by the Danish Medicinal and Chemical Company, Medicinalco.

The therapeutic investigations were concerned only with polycythaemia vera. This relatively benign disease, with its rather long course, would seem to be a particularly appropriate one for a treatment which is of a compensatory nature. We have treated six patients. Only patients whose disease was of several years' standing were chosen. Most of them had already received other treatment such as *x* rays, intravenous nitrogen mustards, or repeated venesection. None of the patients had had any treatment within the nine months before the administration of β-naphthyl-di-2-chloroethylamine was begun.

The clinical histories are concisely recorded because the emphasis is on the haematological changes.

Case 1

A man aged 69 was known to have had polycythaemia for five years, with the red cells around 7,500,000 per c.mm. He received three series of nitrogen-mustard injections intravenously (methyl-bis-β-chloroethylamine), with good results subjectively and objectively. The remissions lasted four to six months after the first two series of injections, but 16–18 months after the third.

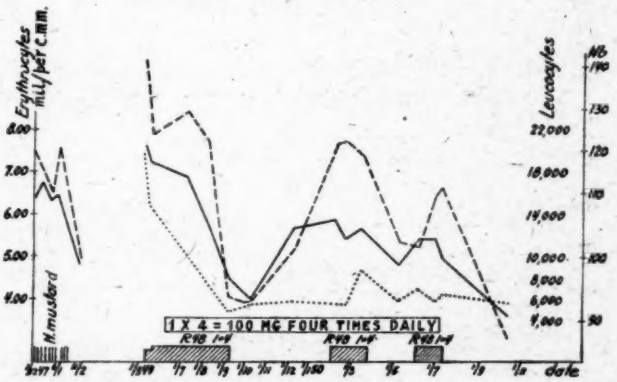

FIG. 1.—Case 1. The dotted line represents leucocytes, the continuous line haemoglobin, and the broken line erythrocytes in this and later figures.

In May, 1949, oral administration of β-naphthyl-di-2-chloroethylamine was begun in doses of 100 mg. four times daily, which each time produced a considerable remission in the blood picture (Fig. 1), and there was an improvement subjectively and a decline in the polycythaemic appearance. A moderate degree of spleen enlargement also disappeared at the same time.

Case 2

A woman aged 49 was known to have had polycythaemia for five years. When the disease was diagnosed the red cells were 7,700,000 per c.mm. She had earlier been treated unsuccessfully with urethane, but later nitrogen mustard intravenously produced a good result, the remission lasting for 15 months.

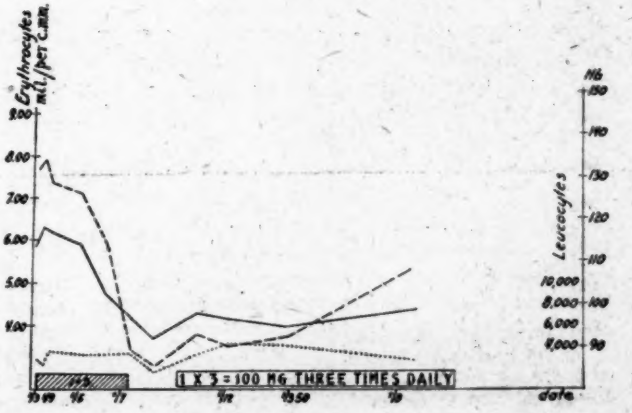

FIG. 2.—Case 2.

As it was impossible to penetrate into her veins, oral administration was started in March, 1949, with β-naphthyl-di-2-chloroethylamine, 100 mg. three times daily, which she received for 126 days. The redness and lassitude disappeared concurrently with a marked fall in the red-cell count and haemoglobin value (see Fig. 2), which have so far remained normal for 15 months since the termination of the treatment.

Case 3

A man aged 51 was known to have had polycythaemia for nine years. He had previously received *x*-ray treatment alternating with venesection, with temporary good effect. In April and May, 1947, he was treated with two series of intravenous injections of nitrogen mustard, which had a good subjective effect but only a slight effect on the blood.

After a lapse of nine months treatment was resumed in November, 1948, with β-naphthyl-di-2-chloroethylamine, 100 mg. thrice daily by mouth. It could be given for only 48 days, as the supply of the drug gave out. Except

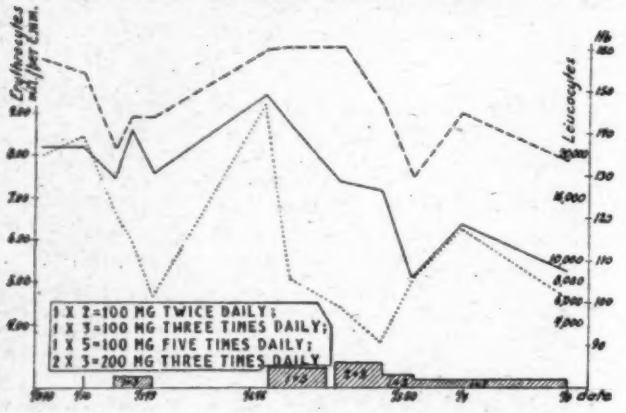
Erythrocytes mill./per c.mm.
Leucocytes
Hb
1 X 2=100 MG TWICE DAILY;
1 X 3=100 MG THREE TIMES DAILY;
1 X 5=100 MG FIVE TIMES DAILY;
2 X 3=200 MG THREE TIMES DAILY
date

FIG. 3.—Case 3.

for a fall in the leucocytes no haematological changes occurred after this dosage, though the spleen enlargement disappeared and the redness was somewhat less.

From July, 1949, the patient has been treated *continuously* with β-naphthyl-di-2-chloroethylamine. For the first three months 500 mg. daily was given, then 600 mg. for two months, and after that 200 mg. daily, on which dose the patient has been kept for 10 months; it is planned to keep him on continuous treatment. In addition to marked haematological improvement (see Fig. 3) his appearance has altered much, the redness having decreased quite considerably.

Case 4

A man aged 61 was known to have had polycythaemia for four years. He has had four series of intravenous injections of nitrogen mustard with temporary benefit. The remissions lasted two to five months.

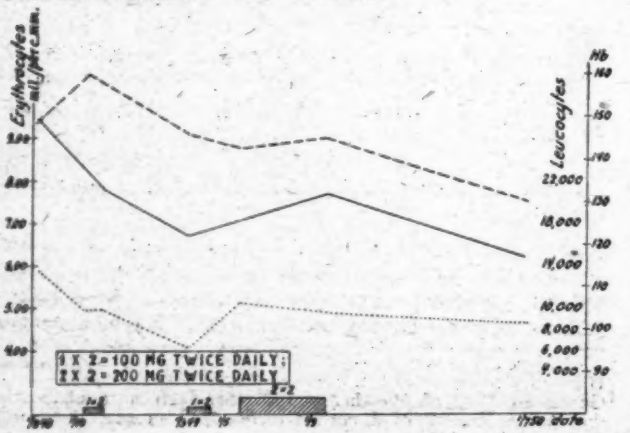

FIG. 4.—Case 4.

After a lapse of ten months treatment was started again in October, 1948, with β-naphthyl-di-2-chloroethylamine, 100 mg. twice daily. This low dosage was given for only 21 days because of short supplies, and no definite effect followed. Later he received 400 mg. daily for four months, but the haematological improvement was only minimal (see Fig. 4), although he himself felt well in the year following the last series of the treatment. A rather considerable enlargement of the spleen persisted unchanged during the treatment.

Case 5

A woman aged 68 was known to have had polycythaemia for four years. She has twice been treated with intravenous injections of nitrogen mustard. The remissions lasted for only five and four months respectively.

In February, 1950, treatment was begun with β-naphthyl-di-2-chloroethylamine, 400 mg. and, later, 600 mg. daily. The treatment was discontinued after 67 days on account

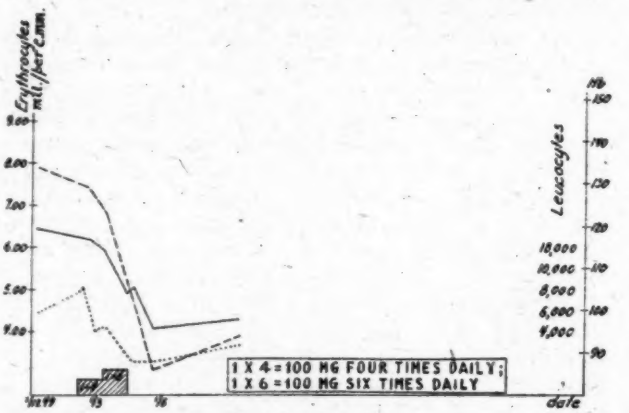

FIG. 5.—Case 5.

of leucopenia (1,200 leucocytes per c.mm. with 82% granulocytes). There was a continued fall in the haemoglobin percentage and red-cell counts, accompanied by a distinct diminution in the patient's polycythaemic appearance, and her dyspnoea and lassitude improved. So far the remission has continued for six months.

Case 6

A man aged 53 was known to have had polycythaemia for three years. He has had intravenous injections of nitrogen mustard four times, with distinct but temporary remissions of up to five months' duration.

In January, 1950, treatment with β-naphthyl-di-2-chloroethylamine was begun at a time when he was greatly troubled by his complaint and had a red-cell count of 9,800,000. To start with he received 300 mg. daily, and later 600 mg. daily for four months, after which the dose was reduced to 200

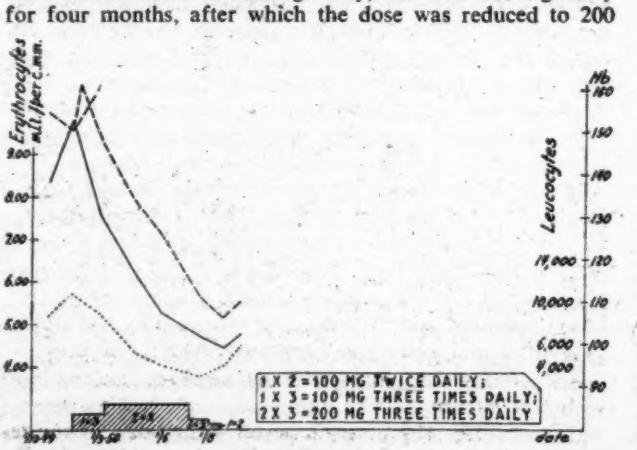

FIG. 6.—Case 6.

mg. daily; we shall try to keep this patient on this dosage continuously.

Fig. 6 shows a marked remission in a haematological respect. A change in the patient's polycythaemic appearance could also be clearly seen.

Comment

The short clinical histories and the diagrams show that a distinct remission occurred in at least five out of six polycythaemic patients in response to the oral administration of β-naphthyl-di-2-chloroethylamine for periods varying from a few weeks up to a few months. At first we were cautious with the dosage; 500–600 mg. might be given daily to start with for a few months, after which the dose should be reduced. An attempt was made to keep two patients stable on a small continuous dose (200 mg. daily), so far with good result.

We have also seen a fall in the leucocyte values during the treatment; in one case a fall to as low as 1,200 leucocytes per c.mm. occurred, but a spontaneous and rapid rise set in 12–14 days after the drug was discontinued.

It appears from this and what was earlier stated that the substance is a potential bone-marrow poison inherent in which is the risk of damage to the bone marrow, with aplastic anaemia or perhaps rather granulocytosis as a result. It is therefore necessary that these patients should be carefully and constantly followed with blood counts during treatment. As is known, polycythaemia is in itself a relatively benign disease and usually the patients have a fairly long expectation of life (cf. Dameshek (1950) and Videbæk (1950), amongst whose groups of patients there were several with a history of over 20 years), and therefore emphasis must be placed on caution during the treatment.

Summary

Six patients with long-continued polycythaemia were treated orally with β-naphthyl-di-2-chloroethylamine. The dosage was between 300 and 600 mg. daily. Treatments were given in series; in only two patients was it possible to give the drug continuously. In five out of the six cases a marked fall in the percentage of haemoglobin and red-cell counts occurred, and, parallel with this, a decrease in the redness and a subjective improvement. In one of the patients the remission has so far lasted for 15 months.

Attention is directed to the toxic effect of the substance on the bone marrow, which necessitates careful and constant control by blood examinations. Gastro-intestinal symptoms were not observed during our tests with the substance.

ADDENDUM

Follow-up, April, 1951

Case 1.—Hb, 106%; erythrocytes, 4,710,000; leucocytes, 8,000. The patient feels well. No erythrosis of the face. Has been without treatment for seven months.

Case 2.—Hb, 106%; erythrocytes, 4,590,000; leucocytes, 5,300. The patient feels well. No erythrosis of the face. Has been without treatment for 19 months.

Case 3.—Hb, 135%; erythrocytes, 5,620,000; leucocytes, 12,900. The patient feels well. Face less erythrotic. Is under permanent treatment with 300 mg. daily, and has been so for 14 months.

Case 4.—Hb, 113%; erythrocytes, 6,020,000; leucocytes, 10,900. The patient feels wells. Face less erythrotic. Has been without treatment for 20 months, but because of the enlarged spleen the treatment will be continued.

Case 5.—Hb, 107%; erythrocytes, 5,160,000; leucocytes, 4,400. The patient feels well. No erythrosis of the face. Has been without treatment for 10 months.

Case 6.—Hb, 126%; erythrocytes, 5,850,000; leucocytes, 5,700. The patient feels well. Has been without treatment for five months, but because of the rise of haemoglobin the treatment will be continued.

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OBSERVATIONS ON ALL BIRTHS (23,970) IN BIRMINGHAM, 1947*

IV. "PREMATURE BIRTH"

BY

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Our objects in this communication are, first, to present evidence on the mortality experience of a large series of births, and, secondly, against the background of this information to comment on the current conception of "prematurity." The use of weight as an index of maturity is so firmly rooted in contemporary practice that the strongest of reasons would be needed for changing it. We shall suggest reasons for reconsidering it, recognizing that on a matter of this kind the last word is not with the research worker but with the practising obstetrician and paediatrician.

It may be useful to recall briefly the circumstances in which the word "premature" was given a precise meaning. Ylppö (1920) suggested that births of infants less than 2,500 g. in weight should be considered not mature, in the sense that they had not remained long enough in the uterus. He justified the use of weight as an index of maturity on the grounds that it was as good as or better than any single alternative, and explained that the limit of 2,500 g, though quite arbitrary, was one below which most births were not fully developed. He recognized that the word "premature" was unsatisfactory, but thought that as it was well established in the literature it would be wise to retain it.

It should be noted that these views were not based on information about a large series of births; Ylppö himself reported on only 670 individuals. Nevertheless had his proposal been seriously in error it seems certain

*This research was assisted by a grant from the Birmingham University Students' Social Services Fund. Parts I (Duration of Gestation), II (Birth Weight), and III (Survival) are published in the *British Journal of Social Medicine* for October, 1950, and April and July, 1951.

that subsequent experience would have exposed it. But the question to be considered is not only whether weight is a useful index of maturity but whether in all circumstances it is preferable to any alternative. A confident answer cannot be given without more data than have hitherto been available.

We have previously recorded observations on all single births in Birmingham during 1947, and have described sources of information on the three issues here examined in relation to premature birth: duration of gestation, birth weight, and the history of survival. It will suffice to state that birth weight was recorded for domiciliary as well as for hospital and nursing-home births, and that the duration of gestation was estimated from the date of birth and the date of the first day of the last menstrual period as given in antenatal documents. We have not used records in which an approximate date was given, nor have we accepted the mother's statement as recorded after the birth of the child. This does not of course eliminate all sources of error, but it ensures that the observation is as accurate as can be obtained from existing documents.

The requisite information was available for 17,072 births delivered after the end of the 28th week, whose distribution by duration of gestation is compared in Table I* with the largest series previously recorded in the literature (Hosemann, 1948). The comparison is made because doubts are sometimes expressed about the consistency of observations on the duration of gestation. For reasons elsewhere discussed (McKeown and Gibson, 1951) we excluded 323 births, and other tables are based on records of 16,749 deliveries.

TABLE I.—*Distribution of Births by Duration of Gestation. A Comparison of Birmingham Data with Data Published by Hosemann (1948)*

Duration of Gestation (Week)	Birmingham, 1947		Data Published by Hosemann	
	No.	%	No.	%
29,30*	54	0·32	43	0·36
31,32	104	0·61	74	0·62
33,34	196	1·15	128	1·07
35,36	442	2·59	312	2·62
37,38	1,197	7·01	816	6·85
39,40	4,879	28·58	3,868	32·46
41,42	7,803	45·71	5,292	44·41
43,44	1,922	11·26	1,114	9·35
45,46	353	2·07	218	1·83
47,48	87	0·51	32	0·27
49,50	31	0·18	20	0·17
51,52	4	0·02	—	—
Total	17,072	100	11,917	100

$\chi^2 = 77{\cdot}92$, n = 11, $p < 0{\cdot}0001$

* Week 29 = 196–202 days.

TABLE II.—*Distribution of "Premature" and Not "Premature" Births by Duration of Gestation*

Duration of Gestation (Week)	Births 5½ lb. (2·5 kg.) and Under			Births over 5½ lb. (2·5 kg.)		
	No.	%	Cumulative %	No.	%	Cumulative %
29	16	1·61	1·61	—	—	—
30	16	1·61	3·22	—	—	—
31	23	2·31	5·53	—	—	—
32	46	4·63	10·16	4	0·02	0·02
33	42	4·22	14·38	2	0·01	0·03
34	66	6·64	21·02	10	0·06	0·09
35	71	7·14	28·16	40	0·25	0·34
36	89	8·95	37·11	177	1·12	1·46
37	98	9·86	46·97	337	2·14	3·60
38	108	10·86	57·83	654	4·15	7·75
39	106	10·66	68·49	1,379	8·75	16·50
40	130	13·08	81·57	3,264	20·72	37·22
41	98	9·86	91·43	4,686	29·74	66·96
42	49	4·93	96·36	2,970	18·85	85·81
43	25	2·51	98·87	1,398	8·87	94·68
44	6	0·60	99·47	491	3·12	97·80
45	5	0·50	100	226	1·43	99·23
46	—	—	—	112	0·71	99·97
47	—	—	—	5	0·03	100
All births of known duration of gestation ..	994	100		15,755	100	

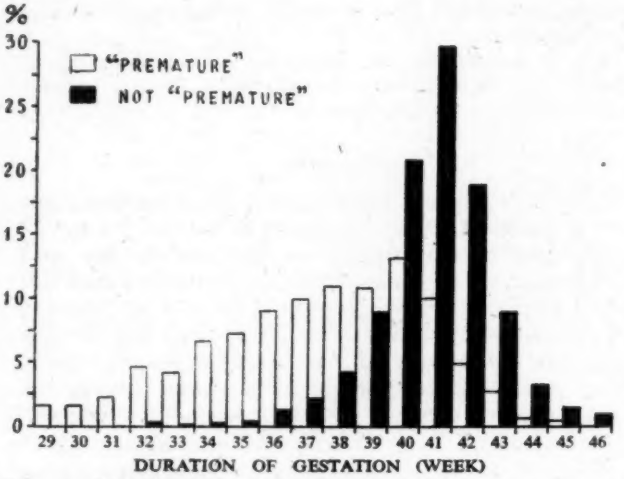

FIG. 1.—Distribution of "premature" and not "premature" births by duration of gestation.

Distribution of "Premature Births" by Duration of Gestation

Writers on "prematurity" have been well aware that not all births below the prescribed weight are born early, in the sense that the duration of gestation is shorter than could be regarded as compatible with full development. This view is consistent with data shown in Table II (see also Fig. 1), which gives the percentage distribution of "premature births" by duration of gestation. More than half the births are born after 37 completed weeks, and about one-third after 39 completed weeks. The percentage of births "premature" at different weeks of gestation is given in Table III (see

TABLE III.—*Percentage of Births "Premature" at Different Durations of Gestation*

Duration of Gestation (Week)	All Births	Births 5½ lb. (2·5 kg.) and Under	
	No.	No.	%
29	16	16	100·0
30	16	16	100·0
31	23	23	100·0
32	50	46	92·0
33	44	42	95·4
34	76	66	86·8
35	111	71	63·9
36	266	89	33·4
37	435	98	22·5
38	762	108	14·2
39	1,485	106	7·1
40	3,394	130	3·8
41	4,784	98	2·0
42	3,019	49	1·6
43	1,423	25	1·7
44	497	6	1·2
45	231	5	2·2
46	112	—	—
47	5	—	—
All births of known duration of gestation ..	16,749	994	5·9
All births of known weight	22,454	1,369	6·1

*The low "p" of the χ^2 test is less useful as a comment on the distribution than as a reminder that it is important to distinguish clearly between the magnitude and the significance of the difference.

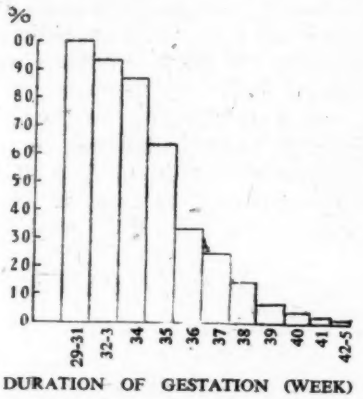

FIG. 2.—Percentage of "premature" births at different weeks of duration of gestation.

also Fig. 2), and as would be expected it decreases fairly rapidly as the duration of gestation increases. Nevertheless about 14% of births delivered in the 38th week are "premature."

Survival Related to Weight and Duration of Gestation

Tables IV and V show the relation of birth weight and duration of gestation respectively to the proportion of stillbirths and neonatal deaths. (In Table IV, in which the duration of gestation is not considered, we have been able to use records of all births of known weight—22,454.) The data require no detailed comment, but we may here note two points the significance of which is discussed more fully below: first, that mortality is so closely related to both weight and duration of gestation that there is little to choose between them as indices of the probability of survival; and, secondly, that births less than 5½ lb. (2.5 kg.) have very different death rates according to their weight at birth.

TABLE IV.—*Percentage of Births Stillborn or Dead in the First Month of Life Related to Birth Weight*

Birth Weight (lb.)	(kg.)	Number of Total Births (*a*)	Still-births (*b*)	Neonatal Deaths (*c*)	(*b*) + (*c*) as Percentage of (*a*)
1–	0·45–	4	2	2	100·0
1½–	0·68–	19	11	8	100·0
2–	0·91–	49	23	22	91·8
2½–	1·13–	60	30	20	83·3
3–	1·36–	68	25	18	63·2
3½–	1·59–	89	29	19	53·9
4–	1·81–	170	31	22	31·2
4½–	2·04–	223	28	14	18·8
5–	2·27–	580	42	37	13·6
5½–	2·49–	977	31	34	6·7
6–	2·72–	2,107	45	39	4·0
6½–	2·95–	3,080	38	35	2·4
7–	3·18–	4,358	64	39	2·4
7½–	3·40–	3,617	37	23	1·7
8–	3·63–	3,350	34	16	1·5
8½–	3·86–	1,668	14	9	1·4
9–	4·08–	1,127	15	7	2·0
9½–	4·31–	438	3	2	1·1
10–	4·54–	331	7	2	2·7
10½–	4·76–	82	2	—	2·4
11–	4·99–	39	2	1	7·7
11½–	5·22–	11	—	—	—
12+	5·44+	7	1	—	—
Total ..		22,454	514	369	3·9

TABLE V.—*Percentage of Births Stillborn or Dead in the First Month of Life Related to Duration of Gestation*

Duration of Gestation (Week)	Number of Total Births (*a*)	Still-births (*b*)	Neonatal Deaths (*c*)	(*b*)+(*c*) as Percentage of (*a*)
29	16	3	12	93·8
30	16	8	5	81·3
31	23	8	9	73·9
32	50	17	17	68·0
33	44	13	10	53·2
34	76	18	14	42·1
35	111	9	12	18·9
36	266	23	17	15·0
37	435	28	13	9·4
38	762	26	15	5·4
39	1,485	45	28	4·9
40	3,394	51	33	2·5
41	4,784	59	39	2·0
42	3,019	31	31	2·1
43	1,423	37	8	3·2
44	497	11	5	3·2
45	231	6	3	3·9
46	112	4	2	5·4
47	5	—	—	—
Total ..	16,749	397	273	4·0

The Conception of "Premature Birth"

If it is difficult to write clearly about "premature birth," as it undoubtedly is, the reason is partly that the conception itself is neither clear nor precise, and it may help to clarify what follows if we state at the outset the ideas which seem to lie behind it. It is well known that pathological examinations invariably attribute a considerable proportion of stillbirths and neonatal deaths to the fact that labour has occurred too early, with the result that the foetus is not mature enough to survive, and dies either during labour or shortly after delivery. In some cases there is an explanation for the premature onset of labour—for example, a multiple pregnancy or the presence of a congenital malformation—in respect of which the question of early birth is a secondary consideration. But in many cases no such explanation is forthcoming, and on the face of it death is preventable (*a*) if the pregnancy can be carried on to term, or (*b*) if the live-born child can be kept alive for a reasonable period after birth. It is the latter problem which challenges the clinician and research worker, not only because such infants may be expected to enjoy good health if they survive (so far as we can judge from present evidence), but also because we have at present no grounds for optimism about some of the other major causes of early death.

As clinical criteria of maturity are difficult to interpret uniformly, particularly when deliveries are conducted by persons other than doctors, it was clearly desirable to agree if possible on a simpler index of the state of development of the newborn infant. The most useful was undoubtedly birth weight. Of the two obvious alternatives, length is a more accurate index of maturity, but in the newborn this observation presents considerable technical difficulties; duration of gestation cannot be relied on in some cases and cannot be given at all in others (15% in our experience*). Weight, on the other hand, can be recorded easily and reliably, in hospital to the nearest ounce, and in domiciliary practice to the nearest quarter pound if portable spring balances are used with reasonable care. There is thus nothing to criticize in Ylppö's suggestion that, as a rough guide to the maturity of the foetus, birth weight is at least as useful as any single alternative. Certainly our own data do not conflict with this view.

Moreover, objections to the use of weight on other grounds are unlikely to prevail against thirty years' experience, unless they can be shown to suggest a different procedure which offers practical as well as theoretical advantages. Any alternative proposal, if it is to be considered seriously, must therefore take account of the two purposes served by the present convention; first, its administrative use as a yardstick for the

*This figure is based on hospital births. Duration of gestation was unknown in a higher proportion of domiciliary births, but only because we were less successful in tracing the antenatal documents.

identification of infants exposed by their early birth to increased risk of stillbirth or infant death; and, secondly, its use in research. We shall consider each of them in turn.

1. "Premature Birth" as an Administrative Device

The data recorded in this communication suggest two observations on the standard procedure as an administrative device—one on the limit of 2,500 g. (5½ lb.), and the other on the invariable use of weight in preference to other criteria of maturity.

Table IV underlines what is of course well known—namely, that the 5½ lb. (2.5 kg.) limit groups together births which have very different prospects of survival (100% of births under 2 lb. (0.9 kg.) were stillborn or died before one month, as compared with 14% of births between 5 and 5½ lb.—2.3 and 2.5 kg.). In so far as the object is to focus attention on a large class (approximately 6% of all births) whose collective risk of stillbirth or neonatal death is about 30%, this may not matter; in so far as it is to identify births for which certain routine precautions are both necessary and practical, the procedure is clearly unsatisfactory. For example, in reports on "premature birth" (Ministry of Health, 1949) Crosse and Miller agree that it is not practical to admit to hospital all live-born children below the prescribed weight, and suggest respectively that babies which weigh more than 4 lb. (1.8 kg.) and 3½ lb. (1.6 kg.) can as a rule be cared for at home. In this case the limit of 5½ lb. (2.5 kg.) is too high to serve as an administrative yardstick without reference to other criteria. The point is of considerable practical importance, particularly in countries such as Great Britain, in which a high proportion of all deliveries are conducted at home.

The second point, and it is the more important, is that the use of weight as an index of maturity fixes attention on the vulnerable infant rather than on the pregnancy which gives rise to it. The fact that an estimate of the duration of gestation sometimes cannot be given with confidence has diverted attention from the very real use to which this important observation, for all its attendant difficulties, can be put. Data shown in Table V leave no doubt that, by using the antenatal record of the date of the first day of the last menstrual period and the date of birth, an estimate of the duration of gestation can be made which, whatever errors are involved, provides as sensitive an index of the risk of death as does the weight at birth. (That the observation cannot be recorded for all births need not discourage us from using it when it is available; moreover, the proportion of accurate records could undoubtedly be increased if the information were considered important.)

No doubt it would be agreed that when the risk of foetal death is high the mother should be admitted to hospital before the birth of the child, not only because the labour can be conducted under more favourable circumstances but also because the infant can be protected more effectively if born alive. The importance of the evidence in Table V is that it enables us, once labour has begun, to anticipate with some confidence the probability of stillbirth or neonatal death, and so can be used as the basis of administrative procedure. The procedure we suggest for consideration is as follows:

(1) That mothers in whom the onset of labour occurs more than four weeks before the expected date should be admitted to hospital.

(2) That live-born infants born at home should be admitted to hospital if they weigh less than 4 lb. (1.8 kg.) at birth.

We can illustrate the effect of these proposals on births in Birmingham during 1947.

Table VI gives the number of births delivered prior to each week of gestation, at home, in hospital, or in nursing-home. Two hundred mothers in whom labour began more than four weeks before the expected date were confined at home (just over 1% of the total of 16,749 births), which measures the additional burden on hospitals if the scheme were implemented.* When we recall, however, that roughly half of all deliveries were in hospital, and that the combined risk of stillbirth and neonatal death for all hospital births was only about 5%, it seems reasonable to suggest that these vulnerable births should have a high priority for institutional delivery. Approximately one in three of them was stillborn or died in the first month, and (as shown in Table V) even in the week with the lowest death rate (the 36th) the percentage of deaths was 15%.

TABLE VI.—*Numbers of Births Delivered Prior to Each Week of Gestation*

Weeks Before Expected Date	Duration of Gestation (Week)	Domiciliary	Hospital	Nursing-Home	Total
12	29	4 (0·02)	12	—	16
11	30	7 (0·04)	23	2	32
10	31	17 (0·10)	36	2	55
9	32	32 (0·19)	71	2	105
8	33	43 (0·26)	102	4	149
7	34	64 (0·38)	153	8	225
6	35	98 (0·58)	226	12	336
5	36	200 (1·19)	378	24	602
4	37	377 (2·25)	619	41	1,037
3	38	681 (4·06)	1,045	73	1,799
2	39	1,331 (7·95)	1,783	170	3,284
1	40	2,909 (17·37)	3,373	396	6,678
0	41	5,191 (31·00)	5,497	774	11,462
	42 and over	7,535 (44·99)	8,128	1,086	16,749

Figures in parentheses express births delivered at home as a percentage of all births (16,749).

Table VII compares weight distributions of all domiciliary births and of domiciliary births delivered after the end of the 36th week. The implementation of the first proposal would have reduced the number of births under 4 lb. (1.8 kg.) delivered at home from 47 to 12. Nine of the 12 were live-born, and would have been admitted to hospital as a result of the second proposal.

TABLE VII.—*Weight Distributions of Domiciliary Births*

Birth Weight lb.	kg.	All Domiciliary Births No.	%	Domiciliary Births Delivered After the End of 36th Week No.	%
1–	0·45–	3	0·04	—	—
2–	0·91–	6	0·08	—	—
2½–	1·13–	11	0·15	4	0·05
3–	1·36–	13	0·17	1	0·01
3½–	1·59–	14	0·18	7	0·10
4–	1·81–	31	0·41	18	0·25
4½–	2·04–	46	0·61	24	0·33
5–	2·27–	148	1·96	114	1·55
5½–	2·49–	222	2·95	202	2·75
6–	2·72–	591	7·84	569	7·76
6½–	2·95–	849	11·27	828	11·29
7–	3·18–	1,489	19·76	1,478	20·15
7½–	3·40–	1,193	15·83	1,178	16·06
8+	3·63+	2,919	38·74	2,912	39·70
Total ..		7,535	100	7,335	100

*The percentage of domiciliary deliveries is actually a little higher, since, as has been stated, the proportion in which the duration of gestation was unknown was greater than in the case of hospital births.

2. "Premature Birth" as a Subject for Research

The issues so far discussed are related to administrative procedure, and have their main application in countries where many deliveries occur at home. Of even wider significance is the identification of birth weight with maturity for the purposes of investigation, which has resulted in an extensive literature ostensibly devoted to the subject of "prematurity."

From the point of view of effective research any convention is unfortunate which obscures differences by dealing collectively with problems which are different in origin. No doubt at an earlier stage in our knowledge it was worth recording certain observations on all stillbirths, or on all congenital malformations; but the day is past when anything useful can be added by investigations which fail to distinguish the separate issues which these terms embrace. The same considerations apply, *mutatis mutandis*, to the subject of "premature birth."

As an administrative device the use of weight as an index of maturity has the advantages and disadvantages to which we have referred; as a means of identifying an entity suitable for inquiry it could hardly be less satisfactory. From the point of view of the investigator interested in the aetiology of stillbirths and infant deaths, it is hard to see that any useful purpose is served by a convention which brings together such completely different subjects as congenital malformations, multiple births, toxaemia of pregnancy, trauma, induction of labour, and early onset of labour of unexplained origin. For it is deceiving oneself to suppose that progress can be made in prevention of "premature birth" due to congenital malformations, except through prevention of congenital malformations. This possibility is not yet in sight, but it can be delayed only by a practice which groups malformations with other causes of death. Similarly the early onset of labour in multiple pregnancies is an observation of considerable biological interest which will not be advanced without separate study of multiple births. Moreover, the confusion of these problems has diverted attention from cases in which the early onset of labour is unexplained, and is hence still the matter of primary interest.

What has been explored in the literature as "premature birth" is the subject of low birth weight; it is hardly surprising that investigation has not been particularly fruitful. If the administrative proposals made above, or some modification of them, commend themselves to clinicians, the research worker need have no regrets if the present conception of "premature birth" were abandoned. He could then return to the study of late foetal development and its relation to the duration of gestation. On this important issue we have as yet very little worth-while evidence.

Summary

Birth weight, duration of gestation, and the history of survival are recorded for 16,749 single births in Birmingham during 1947. The data are used to give: (1) The distribution of "premature births" by duration of gestation. More than half were delivered later than the end of the 37th week and about one-third later than the end of the 39th week. (2) The proportion of births "premature" in different weeks of gestation. (3) The percentage of births stillborn or dead within one month of birth related (*a*) to birth weight, and (*b*) to duration of gestation. It is shown that mortality is so closely associated with both birth weight and duration of gestation that there is little to choose between them as indices of the probability of survival.

The conception of "premature birth" is discussed in the light of these observations, which are used to suggest for consideration a possible modification of administrative procedure as follows. (1) Mothers in whom the onset of labour occurs more than four weeks before the expected date should be admitted to hospital. (2) Live-born infants born at home should be admitted to hospital if they weigh less than 4 lb. (1.8 kg.) at birth.

The effect of these proposals is exhibited on the Birmingham data. The first would have resulted in the admission of an additional 200 mothers (just over 1% of 16,749), whose confinements were in weeks in which the risk of stillbirth or foetal death is about one in three. It is suggested that these vulnerable births should have a high priority for institutional delivery, as nearly half of all deliveries in the city were in hospital, and the incidence of death (stillbirth or neonatal) in all hospital births was only one in twenty.

The operation of the first proposal would have reduced the number of births under 4 lb. (1.8 kg.) delivered at home by about three-quarters.

We are greatly indebted to Dr. Jean Mackintosh and her colleagues in the City of Birmingham Maternity and Child Welfare Department for the facilities which they have placed at our disposal.

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THE NATURAL HISTORY OF VENOUS THROMBOSIS

BY

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[WITH SPECIAL PLATE]

In 1856 Virchow described the mechanical effects of embolism; in 1889 Cohnheim showed that injury to vascular endothelium was favourable, if not essential, to thrombosis; and in 1909 Aschoff discussed the possible influence of eddies in the blood stream. Belt, in 1934, ruled out inflammation as a frequent cause of thrombosis and put pulmonary embolus into its correct category as a medical rather than a surgical complication. These are the milestones of a century in which the accumulated knowledge on the subject might be summarized as: if the venous endothelium is damaged then thrombosis and embolism may occur. It is a philosophical aphorism that when a problem is accurately stated the solution is near to hand. The purpose of this paper is to analyse the natural history of thrombosis so far as is possible by the histological method—a most neglected field—and so to endeavour to close, if only in a minute degree, the vast chasm between our knowledge and our control of a complication which so often kills those who might otherwise recover.

When a student I was taught that thrombosis and embolism were usually surgical complications, but very little observation was required to show that this conception was false and that they were in most cases associated with medical conditions such as congestive heart failure.

As a pathologist I very much doubted whether the concept of acute massive thrombosis was as simple as it seemed. A survey of the literature showed that all workers had neglected the histology of the venous system, apparently because signs of inflammation were unusual. They completely overlooked the obvious fact that the appearances of a thrombus at any given time are determined by its historical evolution. However ordinary may be the aspect, every thrombosed vein must bear the evidence of past history and, within limits, the future progress may be deduced. Accordingly in 130 consecutive unselected necropsies the venous system was carefully examined, with special reference to the main leg veins and their intramuscular tributaries. The necropsies were those of a general hospital with a preponderance of elderly patients; consequently only three were aged 40 or under, and the youngest was aged 12.

Technique

A brief account of the technique adopted is required. In addition to the routine complete necropsy the axillary, pelvic, and femoral veins were carefully examined and the calf muscles and posterior tibial vessels were excised and sectioned after a preliminary overnight fixation in formol–saline to secure cohesion of the muscle fibres. Blocks of muscle for histological examination were taken in all cases and when gross thrombi were present the firm adherent portions were sectioned and also any apparently thickened areas of vein. Cross-sections of the soleus muscle were taken for examination of the small intramuscular veins. In a few instances the deep veins of the foot were examined and thrombi were found, but as they presented no special features the main investigation was confined to the veins of the leg. Control blocks were also taken from the pectoralis major, deltoid, and triceps muscles. Sections were stained by haematoxylin and eosin, iron haematoxylin, and van Gieson, and in some instances by phosphotungstic-acid/haematoxylin and by Wilder's silver impregnation method. When necessary, serials were examined to exclude the possibility of misinterpretation of tissue included in the angle of confluence of venous tributaries.

The macroscopic findings and percentages are close to those of other workers. In 130 necropsies thrombosis of the veins of one or both legs was present in 35 (26.9%), massive pulmonary emboli were found in 13 (10%), and lesser emboli in 7 (5.5%). Any embolus (or emboli) estimated to occlude one-third of the total pulmonary circulation was considered massive.

The histological appearances were much more significant, and, so far as I know, have not previously been recorded. Of the 35 examples of venous thrombosis 19 (54.2%) showed evidence of recurrent thrombosis, and 12 of these had given rise to embolism. In the remaining 16 instances there was no evidence of previous thrombotic attacks, and in this group 8 had shed emboli. Of the 13 massive emboli 8 came from sites of recurrent thrombosis.

Histological Criteria

The concept of acute thrombosis in the generally accepted form was obviously erroneous, since in most instances it described only the final event in a series which occupied a period of anything from weeks to years. This is of the greatest importance in our approach to treatment, but before the thesis can be accepted the histological criteria must be discussed in detail and the relationships and potentialities of endothelium and connective tissue considered.

The first problem is the age of the thrombus. That can be investigated by the study of tissue related to surgical incisions and by serial biopsy of the organizing clot in traumatized and ligated veins, but this bears no relation to the conditions usually prevailing inside a vessel. Authoritative opinions confine themselves to such statements as "white thrombus is older than red" and "white thrombus is formed in a rapid stream, red thrombus in a sluggish flow." There is some truth in both statements, but as generalizations they are untrue. In the arterial stream the mechanical conditions are such that thrombi can be built up only by slow continuous deposition in the form of a thin lamina which rapidly loses its cellular content, and so white is the prevailing colour. Organization is slow and endothelization of the surface is rarely demonstrable, though Duguid (1948) believes that atheromatous plaques may be formed in this way. In the heart, where the different mechanics of a large cavity and muscular contraction operate, organization is often extremely slow and the approximate duration may be known if it dates from clinical infarction. In veins the coagulum may remain macroscopically red until organization is widespread though irregular; isolated parts whiten probably from exposure to the remaining venous current. Organization certainly proceeds rapidly where the thrombus is adherent to the vein wall, and fibroblastic invasion occurs within four days, while endothelium spreads from the vein over the contiguous surface of the clot. If unchecked, this process continues to eventual organization and recanalization; but initially there is an unstable equilibrium, and a breakdown may result in spread of the thrombus and possibly embolism. There is then no means of accurately dating a thrombus, but extensive organization is evidence of a duration of at least weeks, and, more important, if successive and superimposed layers of organization can be demonstrated then the history is carried much further into the past.

The main histological findings in the intramuscular leg veins, in so far as time is a factor in their production, may be considered under three headings: (1) Early thrombotic lesions (Plate, Figs. 1–3); (2) intermediate organizing lesions (Figs. 4–6); and (3) residual fibrotic lesions (Figs. 7 and 8).

Early Lesions

Figure 1 (Special Plate) is a particularly fine example of the earliest demonstrable thrombus arising as a polyp, about 1.3 mm. in size, from a fibrous and vascularized area in the wall of an intramuscular vein. It is completely covered by endothelium, and organization is mainly peripheral and not confined to the base. The central portion consists of red cells and fibrin. Such lesions may be roughly spherical nodules or may extend as "candle gutterings" along the vein wall. As might be expected, agonal thrombus is often present in these situations.

Fig. 2 shows a lesion based on a fibrotic area in the vein and partially covered by endothelium. The thrombus extended into the main leg veins.

Fig. 3 represents an unendothelized mass of thrombus based on a fibrotic area of vein and extending into the main veins. There is slight basal organization, and pigment-laden macrophages are numerous.

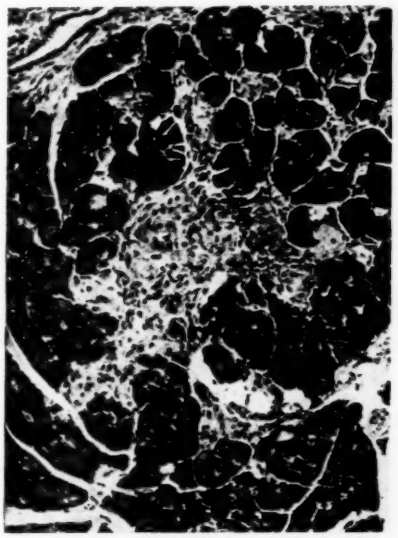


FIG. 1.—Pancreas of rat treated with lactose (controls). Moderate hyperplasia of islets; peri-insular sclerosis. (Cardeza, 1950.)

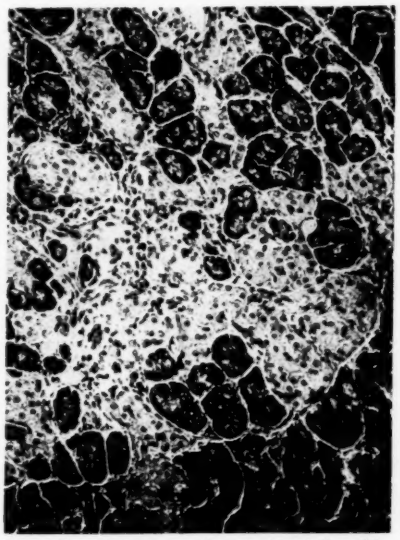


FIG. 2.—Pancreas of rat treated with diethylstilboestrol. Intense hyperplasia, adenomatous. (Cardeza, 1950.)

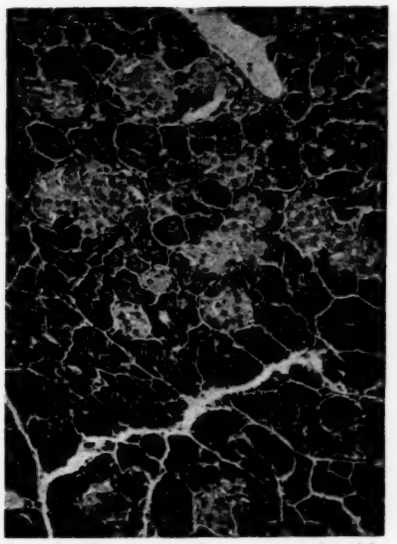


FIG. 3.—Pancreas of rat treated with ethynil-oestradiol. Diffuse hyperplasia of islets. (Cardeza, 1950.)

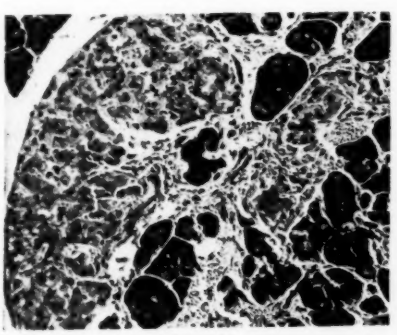
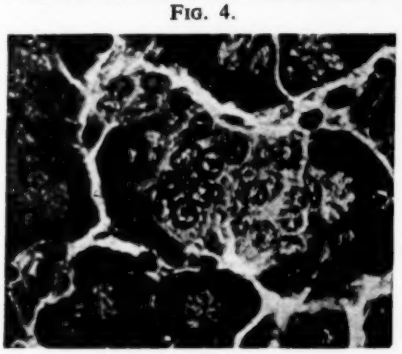


FIG. 4.



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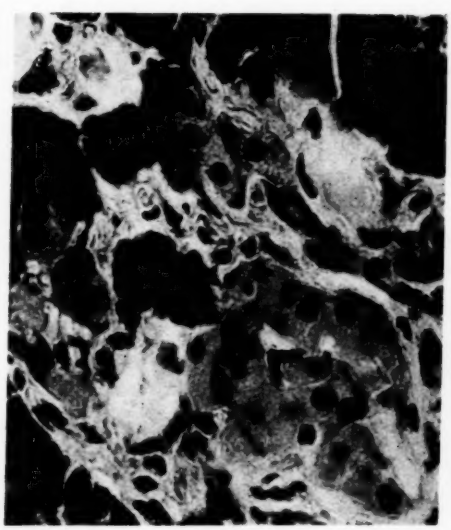


FIG. 6.

FIG. 7.

FIGS. 4–7.—Pancreas of rats treated with diethylstilboestrol. FIG. 4: Adenomatous hyperplasia of insular cells. FIG. 5: Hyperplasia of centro-acinar cells. FIG. 6: Newly formed islets from centro-acinar cells. FIG. 7: Mixed formation acino-insular. (Cardeza, 1950.)

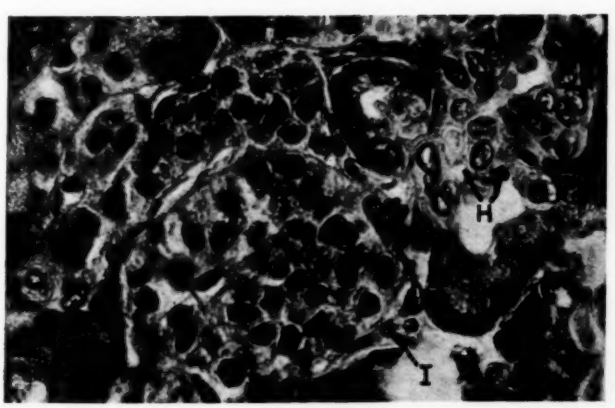


FIG. 8.

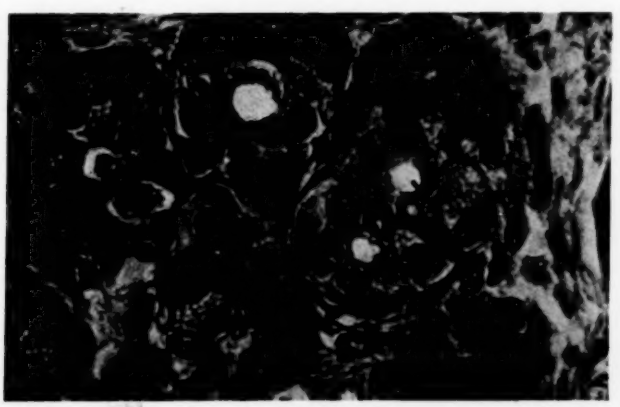


FIG. 9.

FIGS. 8 AND 9.—Local action of oestradiol on the islets of Langerhans of the cat. FIG. 8:—In H: hyperplasia of centro-acinar cells with granulation. FIG. 9: Newly formed centro-acinar cells with granulation. (Cardeza and Rodríguez, 1949–50.)

C. RAEBURN: NATURAL HISTORY OF VENOUS THROMBOSIS

FIG. 1.—Thombus on scar in wall of intramuscular vein. Covered by endothelium; basal and peripheral organization. Central mass of red cells. (H. and E. ×40.)

FIG. 2.—Partially endothelized thrombus from a fibrotic area in vein wall. Slight peripheral organization overiying main mass of red cells and fibrin. (H. and E. ×50.)

FIG. 3.—Thrombus arising from a scar in the vein wall. Note the breach in the media and basal organization. Endothelium has spread a short distance on to the thrombus. (H. and E. ×60.)

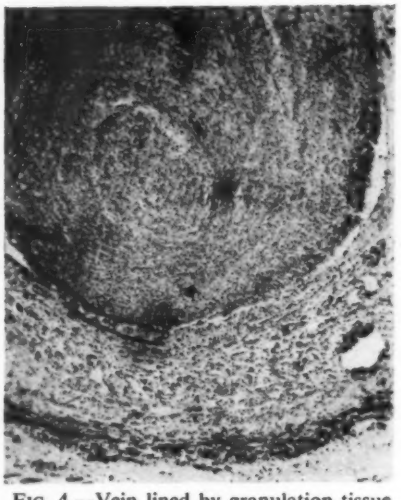


FIG. 4.—Vein lined by granulation tissue, product of fusion of intima with organizing thrombus. Recent thrombus in lumen. (H. and E. ×50.)

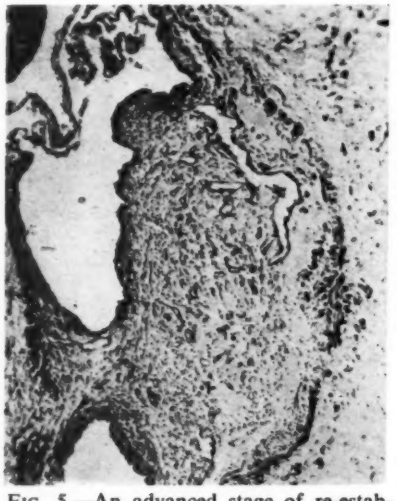


FIG. 5.—An advanced stage of re-establishment of venous channels. (H. and E. ×55.)

FIG. 6.—The final stage in organization of a small discrete thrombus: a vascular and fibrous nodule with a superimposed lamina of organizing thrombus—a second thrombotic sequence. (H. and E. ×55.)

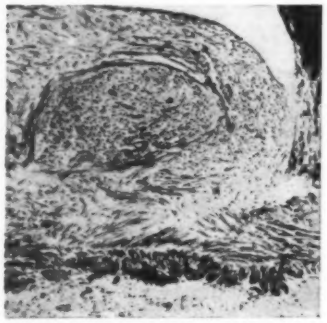


FIG. 7.—Successive zones of thrombosis and organization. (H. and E. ×45.)

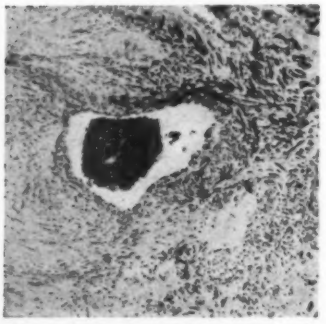
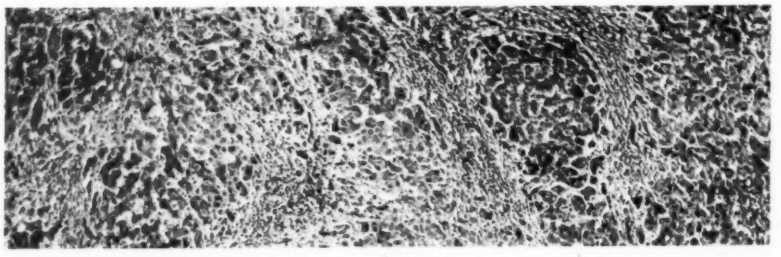
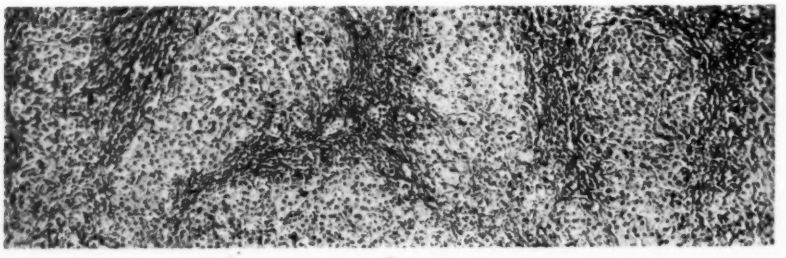


FIG. 8.—Concentric zones of fibrosis indicating three thrombotic events. (H. and E. ×45.)

T. S. L. BESWICK AND H. BUTLER: FATAL HAEMATEMESIS



A



B

FIG. 1.—Low-power views of sections of the liver showing the irregular sheets of regenerating liver tissue. (A) Stained with haematoxylin and eosin. (B) Stained with the Curtis modification of van Gieson's stain.

The important features of this group are: (*a*) The thrombi are more or less covered by endothelium and endothelization precedes organization, except, possibly, in the basal area. (*b*) The lesions are based on previously damaged areas of vein wall as shown by focal muscular atrophy and fibrosis and vascularization of the intima, which may become almost angiomatous in appearance. (*c*) A study of endothelial and fibroblastic proliferation and capillary formation in such a relatively simple histological field affords visual evidence of the identity of fibroblast and endothelial cell. (*d*) The cell pattern suggests that fibroblasts migrate from the basal area peripherally until the surface is reached. Under the impact of a new environment they undergo modification and become endothelial cells. If a new thrombosis occurred fibroblastic potentialities would be reassumed by the surviving cells. Succeeding fibroblasts orientate themselves deep to the endothelium and account for the early peripheral organization.

The simplifying concept of cellular pluripotentiality is widely recognized by histologists, but application to pathological histology has been neglected; hence the persistence of such mythical tumours as the "endothelioma."

Intermediate Lesions

When a layer of mural thrombus in a small vein is able to organize completely the appearances are those seen in Fig. 4. The intima has become vascularized and blended with the organized thrombus, and superimposed on this zone of granulation tissue is recent thrombus. The muscularis has atrophied. The last stage in this phase is a spongy and relatively acellular granulation tissue completely filling the vein. The changes from now on are atrophic and consist of further loss of cellularity, increasing collagenization, and necrosis of connective-tissue partitions so that larger vascular channels are formed (Fig. 5).

Fig. 6 illustrates the end-result in a small discrete thrombus: a raised vascular nodule incorporated in the vein wall upon which is superimposed a layer of more recent organizing thrombus, while agonal clot is present in the lumen. This would be the optimum end-result of the lesion illustrated by Figs. 1 and 2.

Residual Lesions

Fig. 7 is a slightly oblique section through a vein of about 2 mm. diameter. The fibrosed muscularis extends transversely at the lower part of the photomicrograph, and internally are successive zones of organization and recanalization, representing two thrombotic sequences, and, finally, early organization of the recent thrombus, seen on the right-hand side.

Fig. 8 is a similar lesion showing concentric rings of fibrosis in a vein of the same size. The remains of the muscularis are visible on the upper right-hand side. The most cellular and most recent zone of fibrosis is towards the lumen. Excluding the plug of recent thrombus, which is not adherent at this point, there is evidence of three sequences of thrombosis and organization.

Other Findings

The other histological components of muscle can be dealt with briefly.

Nerves.—These show no histological abnormality.

Arteries.—Occasionally intimal fibrosis and atheromatous lesions occur in the larger vessels.

Muscle Fibres.—Invariably oedema, and occasionally diffuse fibrosis and myodegeneration, are present. In one instance there were areas of myodegeneration progressing to necrosis but without cellular reaction, and therefore probably a terminal happening. In another instance there was a focal interstitial myositis of the soleus muscle. The cells are mainly lymphocytes with a few plasma cells, and are grouped round dilated capillaries. The included muscle fibres are basophil-staining and show multiplication of sarcolemma nuclei, suggesting that the cellular infiltration is primary and a stimulus to proliferation. There is no myodegeneration.

One negative finding is of aetiological importance. Thrombosis does *not* occur in veins of a diameter of less than 1 mm. approximately—that is, in veins which are freely anastomotic and without valves.

Lesions were not found in the control sections of muscle from the upper extremity.

Discussion

Certain undisputed facts concerning the initiation of thrombosis have been well known since the days of Virchow and Cohnheim, but the unfortunate pre-eminence ascribed to surgery has been allowed to dominate their critical assessment. The prime cause of thrombosis is simple confinement to bed, particularly in the case of elderly people, and the only way in which surgery contributes to the incidence is by fulfilling this condition and by adding to it other factors conducing to venous stasis, such as immobilization of the leg or restriction of abdominal respiration. In the series here considered many were aged and the clinical notes were not very detailed, so that reference to previous lengthy confinements to bed was not always possible, though obviously such periods are a probability in a long life; it is of interest, however, that of three of the youngest (aged 47, 32, and 12) two (those aged 47 and 32) had a history of duodenal ulcer and several spells of bed treatment, and two (those aged 47 and 12) had rheumatic cardiac lesions. Chronic right heart failure was present in 9 of the 35 examples of venous thrombosis.

Venous stasis, whether due to immobility and muscular atrophy or to right heart failure, or to a combination of these factors, is the most important of the local phenomena, and may, I believe, in itself initiate thrombosis, provided that the metabolism of the vascular endothelium is disordered. I deliberately reject the word "injury" because it suggests necrosis and loss of surface—a venous ulcer as the basis of thrombosis. This is a quite unnecessary postulate. Cohnheim's original statement in 1889 that "as long as the endothelium is intact and performs its function normally the blood will remain fluid in the vessels" has two gross inaccuracies in that it postulates loss of surface and, as he subsequently makes clear, it embodies a teleological concept—the specific dynamic, antithrombotic property of endothelial cells. His second dictum, that "stasis alone cannot induce thrombosis," has been tacitly accepted, and constitutes a bar to progress, as it is quite obvious that congestive heart failure is a great source of damage to all epithelial cells and there is no reason to suppose that endothelial cells are unscathed, though our histological technique may be inadequate to detect the cytoplasmic changes. As an example, albuminuria is not necessarily accompanied by any visible change in the renal epithelium.

Can we, then, explain the formation of thrombus on any particular place in the vascular lining? Trauma must be allowed as a minor cause. Needle puncture

must always cause a minute lesion, and this may in favourable, but fortunately rare, circumstances spread. Sepsis is an occasional and special cause, and need not be considered here. If the veins are engorged and the valves are still efficient strong muscular contraction could produce a great rise in intravenous pressure and cause a tear at the valve commissures. By forcible injection of gelatin containing brilliant green at arterial pressure I have sometimes produced such lesions in the cadaver. At the site of rupture the dye stained the intima. Drinker, Wislocki, and Field (1933) have recorded that the pressure in the afferent lymphatics of the popliteal area of a dog is *nil* at rest but up to 25 mm. of mercury with passive motion. There is at present no means of estimating intramuscular lymphatic or venous pressure during active movement. Certainly thrombosis seems to be confined to veins with valves, but again there is no need to postulate more than a point of biochemical weakness. In the smaller valveless veins the blood is capable of movement by anastomotic channels, and the tissue oxygenation is therefore better.

Platelet adhesiveness has somehow been assigned a causative function, but it is merely a part of the mechanism of the thrombotic reaction and not the prime cause. If, however, we can show that the intimal surface becomes adhesive when biochemically abnormal then the process is readily explained, as two sticky objects will be in contact.

It is well known that collagen is markedly adhesive, as may be shown by spreading and drying areolar tissue on a slide. Day (1947) has demonstrated that this adhesiveness is a property of the cement substance binding the collagen fibres, and it is this substance which undergoes a partially reversible sol–gel reaction if it is treated first with weak acid and then with saline. Vascular endothelium is in direct contact with underlying collagen fibres and, moreover, is derived from the fibroblast. In any granulation tissue fibroblasts can be seen arranging themselves to form vascular channels. The endothelial cell is merely a fibroblast which has assumed new properties in virtue of its position on a surface.

A crude experiment demonstrates the adhesiveness of the underlying collagen. Take two segments of vein or artery—and artery is better because of the added rigidity and thickness—and open them carefully so as not to damage the endothelium. Wash with saline, scratch the centre of one piece with a needle, then press both, intimal surface downwards, on a smooth clean glass surface. Dry off in the incubator overnight and then test the attachment of both portions. The unscarified portion will have detached itself, or will at most be lightly adherent, while the scarified piece will be firmly adherent at the point of damage. This is due to exposure of collagen and local release of the intercollagenous cement substance.

I suggest that biochemical changes in the endothelium allow permeation of this cement substance or that the endothelial cell itself, in virtue of inherent fibroblastic potentials, becomes adhesive, and that this is the primary vascular defect upon which platelet thrombus forms. (If the endothelium be removed from an atheromatous nodule in an artery the exposed necrotic material is intensely adhesive.)

It remains to explain why thrombosis rarely occurs in sites such as the arm. The pelvic and gluteal veins are fairly often thrombosed, but these may be regarded as part of the lower extremity. Thrombosis of the arm veins, when it occurs, is always associated with trauma, sepsis, neoplastic compression, or rigid immobilization. The additional factor required to induce and propagate thrombus is immobility and associated muscular atrophy, which encourages the local oedema and tissue circulatory failure. This factor is present in some degree during any lengthy period of rest in bed, but the arms, throughout the most severe illness, are kept moving almost to the time of death. As a corollary to this, any limb thrombosis is a great rarity in infants, for at that age all four limbs are kept in motion. The only thromboses that I have encountered in the legs of infants were associated with surgical procedures and immobilization of the limb.

The entire process can now be presented in chronological order. The physico-chemical state of the endothelial cell is affected by general or, in some instances, local modification of the blood and tissue fluids and responds by an alteration of surface tension in the direction of adhesiveness. Platelet and red-cell thrombus forms, usually at a great number of points, in the intramuscular and main leg veins. If conditions are unfavourable to the propagation of thrombus these lesions endothelize and organize, and are finally represented by a fibrotic nodule containing large capillaries and a few pigment-laden phagocytes—a common finding in sections of leg veins. If conditions are favourable the thrombus spreads and coalesces with similarly formed thrombi. The third possibility is alternating quiescence and spread as endothelization waxes and wanes in response to the necessary chemical stimuli. From the histological evidence it is probable that a scar in the vein wall is commonly the starting-point of a later thrombotic event.

Embolism becomes an increasing probability as the thrombus increases in size and tends to lie free in the large veins. When this stage is reached the only possible mode of healing is by the establishment of adhesions and by subsequent peripheral organization.

Summary

Histological evidence shows that of thromboses discovered at necropsy 54.2% are built up by successive thrombotic sequences. If the histological criteria of recurrent thrombosis are accepted it will be recognized that error must be in the direction of omission, as it is impossible to examine in detail the entire microvenous system of the leg muscles.

The thesis is therefore advanced that in most instances venous thrombosis in the leg is a chronic additive process and not, as is generally accepted, an acute disorder. The essential lesion is considered to be a modification of the colloid properties of groups of endothelial cells which encourages platelet adhesion.

My acknowledgments are due to Dr. H. Loewenthal, Director of the Pathological Laboratories at Chase Farm Hospital, where the major part of the work was carried out; to Dr. A. B. Bratton, of the Central Histological Laboratory, for enabling me to complete the work; and to Mr. G. W. Moore for the photomicrographs.

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ANGINA IN THE ANALGESIC LIMB

BY

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In order to explain certain observations on pain reference, Cohen (1947) proposed a special hypothesis. His observations were that referred pain could be abolished or diminished by anaesthesia of the homosegmental area, and that it could be produced or increased by hyperaesthesia. He suggested that there was normally a continual stream of subliminal pain impulses coming from the body. In the case of angina the pain impulses from both the heart and the arm would reach a functionally related area in the sensorium and, when integrated with the cortical pattern of the body image, would be localized selectively in that segment. Cohen admitted that this continual stream of subliminal impulses was hypothetical, but claimed that his suggestion had the greatest virtue of a hypothesis—that it could be tested. The following experiments were designed to test it.

Argument

If a mixed nerve is infiltrated with procaine the various fibres are paralysed and recover in a constant order. Pain sensibility and sympathetic vasomotor tone are lost first; next comes temperature sensation; position sense, motor power, and superficial sensation go last and recover first. It should therefore be possible by means of a weak but extensive brachial block to prepare an arm that was analgesic but which had power and other forms of sensibility only slightly affected. If a patient with angina were so treated and the arm pain persisted, then subliminal impulses could have played no part in its production, because they must have been abolished. If pain were so abolished these impulses could still be postulated.

Experimental

The patient was walked over a test course and asked to describe his pain as it developed. The circulation of the arm was then occluded by a blood-pressure bandage and the patient opened and shut his hand till pain became intolerable. The number of these *ischaemic contractions* was noted. He was then shown the degree of pain produced by pin-prick, forced flexion of the fingers, and thumb pressure in the first interosseous web and over the flexor surface of the arm just above the wrist. The brachial block was then performed, sometimes with weak procaine (1%) to get the required degree of paralysis at its height, sometimes with more and stronger procaine to get it in the recovery phase. The technical difficulty is to get all parts of the arm in the same sensory state at the same time. With a satisfactory result no pain could be elicited below the mid-upper arm. Ischaemic contractions could be performed to the stage of paralysis, but without pain. Temperature sensation was usually impaired. Touch and position sense were objectively normal, though the limb might feel clumsy and "different." Power was only slightly affected if at all. Ptosis, a contracted pupil, and a hot red arm were always present.

The patient was then walked over the course again till angina was produced. This always required more effort than before the injection. On return his sensibility was again tested to see that the arm was still in the required state. In eight patients the experiments were technically successful.

Case Reports

Case 1.—An intelligent obsessional Civil Servant aged 49. Ischaemic contractions before injection, 50. Twenty minutes after injection contractions stopped at 80 by paralysis, but no pain. No pain sensibility to other tests. Cotton-wool detected, but impaired. Arm felt clumsy, but power objectively normal and he could do up buttons and distinguish coins. Temperatures were accurately distinguished, but were less intense. After walking about five times as far as before test, angina was felt in chest, arm, and wrist. This was quite definite. The arm pain was as intense as he would have expected from the chest pain, though both were less. *Re-test after experiment:* Ischaemic contractions stopped at 70 by paralysis. No pain to other stimuli. Cotton-wool detected, but more impaired. Hot and cold distinguished only by simultaneous comparison; all called hot when done separately. Position sense and power objectively normal, but the arm felt more clumsy. *Comment:* Perfect analgesia; arm pain not altered.

Case 2.—A man aged 59, not of high intelligence, was very sensitive to pain. He had always had more pain in his arm than in his chest. Ischaemic contractions, 30. Fifteen minutes after injection contractions stopped at 80 by paralysis. Felt slight pin prick everywhere except on the ulnar border. Area of hyperaesthesia over back of thumb and radial border of the wrist. Pain sensibility otherwise absent. Cotton-wool sensation absent over ulnar border, minimal stimuli otherwise detected, but less intense. Position sense and power objectively unimpaired, though he felt that the extensors of the wrist and elbow were weak. Walking was followed by a completely unmodified arm pain, later spreading to the chest in the usual way. *Re-testing:* Ischaemic contractions stopped at 100 by paralysis, otherwise as before the experiment. *Comment:* Perfect analgesia; arm pain not altered.

Case 3.—A market porter aged 42; co-operative, unsuggestible, and of moderate intelligence. Ischaemic contractions, 80. The brachial plexus was almost completely blocked and the test made in the recovery phase. Before the test ischaemic contractions stopped at 125 by paralysis. Did not feel pain with pin-prick or muscle pressure. Power normal except for weakness in shoulder. Distinguished coins, and fine movements performed. Felt all temperatures as warm. Cotton-wool normal, but no tickle except over inner arm. With considerable exertion the chest pain came on and the arm pain a few paces later, just as it always did. *Comment:* Perfect analgesia; arm pain not altered.

Case 4.—A messenger aged 58; a good observer. His left arm was amputated in 1917, and he still has a full-sized movable phantom. The angina came on in the right arm and was never felt in the phantom. It was felt in the arm before it went to the chest. Ischaemic contractions, 50. The brachial plexus was widely infiltrated and the test done in the recovery phase. Before testing pin-prick was dull except over the ulnar border, where it was pointed. No pain with pressure and finger bending. Cotton-wool was normally detected. The hand was still weak and clumsy and he could not do up his tie. After climbing two flights of stairs angina was felt in the chest, but nothing in the arm. After a few minutes' rest he climbed another flight. The usual angina was felt in the arm and then in the chest a few seconds later. *Re-testing:* No pain with pin-prick or muscle pressure. Ischaemic contractions stopped at 60 with pain. Cotton-wool, power, and fine movements normal. *Comment:* Moderate analgesia, power impaired; arm pain not altered.

Case 5.—A married woman aged 31 with mitral stenosis and aortic incompetence; a good witness but a bit frightened. After injection pin-prick was everywhere dull, except slightly pricking over the ulnar border. No pain with muscle pressure or finger bending. Cotton-wool

everywhere normal except definitely impaired over the thumb. Power and position sense normal except that she could not flex her elbow against gravity. Hot and cold could not be distinguished. After a long walk angina was felt in the upper arm. Later it was felt in the chest and then in the elbow. It did not spread to the wrist, as was usual. *Re-testing:* Slight flinching with muscle pressure and finger bending, but much less than normal. Pin-prick was painful in patches in the upper arm and fourth and fifth fingers. Cotton-wool, power, and temperature unchanged. *Comment:* Patchy analgesia, power impaired; arm pain less widespread.

Case 6.—An honest garrulous man aged 42, not very sensitive to pain or good at analysing symptoms. Ischaemic contractions, 100. After injection ischaemic contractions 110, almost paralysed but some deep aching. No pain with muscle squeezing. Pin-prick abolished except possibly for some sensibility in the hand. Cotton-wool always felt, but less than normal. Power and use of hand not affected. After strenuous walking angina was felt in the chest and arm as far as the elbow. The arm pain had the usual distribution and time relationship to the chest pain. Though quite definite, it was not as severe as he would have expected. *Re-testing:* Felt pin-prick "right at the end" all over the arm. Muscle and finger squeezing were just painful at the height of the stimulus. Ischaemic contractions stopped at 100 by pain. Other function unchanged. *Comment:* Incomplete analgesia; arm pain less severe.

Case 7.—A decorator aged 51 was a good intelligent witness, hyperaesthetic. Ischaemic contractions, 55. After injection ischaemic contractions not tested. Completely analgesic to pin-prick and muscle and finger squeezing. Hot and cold not distinguished. Cotton-wool normal except for loss of tickle, especially along the ulnar border. Position sense not affected. Slight general weakness of hand. Did not swing his arm while walking. With walking the chest pain came at the normal point. At the same time there was a detectable pain in the usual distribution of the arm, but it was much weaker than that in the chest, instead of being stronger, as was usual. *Re-testing:* Cotton-wool normal. Temperature nearly normal. Power still impaired. Ischaemic contractions stopped at 110 by severe pain. Muscle and finger squeezing were just painful, though much less than normal. *Comment:* Moderate analgesia, power impaired; arm pain definitely less.

Case 8.—A man aged 46; a very analytical observer of his symptoms. He got pain in both arms equally. Ischaemic contractions, 70. Tested in the recovery phase after fairly complete paralysis. Pin-prick absent except over the central palm. No pain with muscle and finger squeezing. Ischaemic contractions stopped at 100 with paralysis and some tingling pain. Cotton-wool appreciated everywhere, but diminished. Some general muscular weakness. Fairly good distinction of temperature. With hard stepping exercise the pain appeared as usual in the chest and right arm. There was no pain at all in the injected arm. *Re-testing:* No pain with muscle and finger squeezing or pin-prick. Ischaemic contractions stopped at 70 by pain. Otherwise unchanged. *Comment:* Perfect analgesia, with impairment of touch and power; arm pain abolished.

Discussion

In Cases 1 to 4 there was no pain sensibility in the arm and yet the patients felt referred pain there. In Cases 5 to 7 angina was felt in the arm, but the arm was not completely analgesic. Nevertheless, considering the force of the stimulus required to produce pain, it can hardly be argued that subliminal impulses could have played any part. Case 8 gave a contradictory result, and no explanation is offered. It is concluded that hypothetical subliminal pain impulses could have played no part in producing the angina in seven of the eight cases. Although pain sensation was abolished, touch, position sense, and movements were little affected, so that the arms all felt nearly normal. The fact that angina was referred to them is consistent with the view (Harman, 1948) that pain from an unperceived part (for example, the heart) will be referred to a perceived part of the same segment (for example, the arm).

I wish to thank Drs. J. G. Bourne and W. D. Wylie for performing these and other brachial blocks, and the patients themselves for undergoing the experiments.

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FATAL HAEMATEMESIS, FROM OESOPHAGEAL VARICES, IN PRESENCE OF LARGE PORTAL-CAVAL ANASTOMOSIS

BY

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[WITH SPECIAL PLATE]

In recent years operations have been devised to produce large portal-caval shunts in order to prevent haematemesis in cases of portal venous obstruction with gastric or oesophageal varices (Blakemore, 1948; Linton *et al.*, 1948). The following case is reported because it shows a naturally developed shunt which is of the same order of size as those produced surgically and which failed to prevent fatal bleeding.

Collateral vessels are found at the following sites in portal venous obstruction (McIndoe, 1928):

"In classifying these rather numerous channels I have adopted a method given me by Dr. H. A. Harris, of University College, London. It has the advantage of being embryologic in conception and consequently easier to remember than the formidable anatomic lists in textbooks. The channels fall naturally into three groups, according to their situation.

"*Group 1.*—At the two situations in the gastro-intestinal tract where absorbing epithelium comes into contact with protective epithelium—that is, the cardia and the anus. The former represents the site of anastomosis of the coronary vein of the stomach with the intercostal, azygos minor, and diaphragmatic veins of the caval circulation, here producing oesophageal varices. At the latter, the superior haemorrhoidal vein of the portal circulation anastomoses with the middle and inferior haemorrhoidal veins of the caval circulation. Occasionally haemorrhoids develop, though they very rarely become large and are usually not clinically important.

"*Group 2.*—At the site of an obliterated embryonic circulation—that is, in the falciform ligament containing the para-umbilical veins. The umbilical vein is itself rarely, if ever, a part of the actual circulation, being entirely obliterated a few days after birth.

"*Group 3.*—At all situations in the abdomen where the gastro-intestinal tract, its appendages, or the glands developed from it become retroperitoneal developmentally or adherent to the abdominal walls pathologically. This includes the duodenum, small intestine, colon, omentum, spleen and pancreas, containing the veins of Retzius, and the liver

with its accessory veins of Sappey, both establishing an anastomosis between the portal and caval veins. These channels may be increased artificially by operative procedures, as, for instance, by producing adhesions between the liver and diaphragm or by attaching the omentum to the anterior abdominal wall, as in the Talma-Morison operation."

Case Report

A petrol-pump attendant aged 35 was referred to the local chest clinic with a history of having coughed up small amounts of blood over the previous four years. Examination revealed no evidence of pulmonary disease, but screening showed a high right diaphragm. He was referred to Dr. Leslie Cole as a probable case of haemorrhage from oesophageal varices. He had been a prisoner of war in Germany from 1940 to 1945, and during 1945 he was in hospital for several months with pleurisy and jaundice. He stated that a pint (570 ml.) of fluid had been removed from his back. Since 1946 he had suffered from gnawing epigastric pain occurring about half an hour after food. He vomited occasionally, and this relieved the pain. Three days before admission he passed a dark tarry stool; the next day he brought up a little dark blood; and on the evening before admission he vomited 2 pints (1.1 l.) of dark blood.

He was admitted to Addenbrooke's Hospital on August 12, 1950, when examination showed a pale and moderately jaundiced man with a number of telangiectases on the skin of the left arm and chest. The liver was enlarged and the tip of the spleen was just palpable. There did not appear to be any ascites. There were a number of dilated veins running over the costal margins. Rectal examination revealed black semi-fluid faeces but no haemorrhoids.

Investigations.—A barium meal on August 31 and a barium swallow on September 2 were negative. Liver-function tests on August 15 showed: total serum protein, 5 g./100 ml.; serum albumin, 3.3 g./100 ml.; serum globulin, 1.7 g./100 ml.; non-protein nitrogen, 20 mg./100 ml.; alkaline phosphatase, 4.05 Bodansky units (normal 1.5–4); thymol turbidity, 2 units (Maclagen); thymol flocculation, *nil*; serum bilirubin, 4.6 mg./100 ml. On August 14 the prothrombin content was 32% of average normal (Quick, one stage). A blood count on August 14 showed: haemoglobin, 11.1 g./100 ml.; red cells, 3,780,000 per c.mm.; white cells, 8,200 per c.mm. (differential count, normal). The Wassermann and Kahn reactions on August 24 were negative.

During the first 24 hours in hospital the patient vomited 64 oz. (1.8 l.) of blood and passed two melaena stools. During this time he received 5 pints (2.8 l.) of stored blood intravenously without any reaction. His condition improved and the bleeding appeared to have ceased. He made good progress until August 19, when he developed an urticarial rash which responded to mepyramine hydrogen maleate ("anthisan").

On September 1 he began to complain of abdominal pains, and on September 5 he vomited blood, 85 oz. (2.4 l.) in all. One specimen of vomit contained pieces of raw apple. The patient was on a strict ulcer diet and had been forbidden to eat anything not allowed by the diet. He was given 3 pints (1.7 l.) of stored blood, but he remained drowsy and his breath had a "cholaemic" odour. During the next three days he vomited only small amounts of blood, but became increasingly drowsy and irrational. He developed oedema of the right hand and forearm and his lower limbs became spastic. His haemoglobin content fell to 8.5 g. per 100 ml. He died on September 8, death being apparently due to a combination of blood loss and liver failure.

Post-mortem Examination

The liver was considerably enlarged (2,900 g.) and had a finely nodular greenish surface. The cut surface showed fine bands of fibrous tissue surrounding slightly bulging red or yellow areas of parenchyma which were 0.1 to 0.2 cm. in diameter. There were a few larger nodules of soft yellow parenchyma, up to 0.7 cm. in diameter, but these were not conspicuous. The small contracted gall-bladder had a thick wall, but the mucosa appeared normal and it contained apparently normal bile.

The stomach and intestines were filled with blood. The stomach and oesophagus were removed in one piece, and "neoprene latex 601A" was injected into the cut end of the left gastric vein. Dissection, after fixation in formalin, revealed extensive oesophageal varices (Fig. A). The gastric veins were moderately dilated and tortuous. Just above the cardia there were a number of areas of epithelial erosion, approximately 0.1 cm. in diameter, overlying the oesophageal varices. Both the lamina propria and the submucosa contained oesophageal varices. In the former, numerous dilated and thin-walled subepithelial veins extended cranially for about 1½ to 2 in. (3.8 to 5 cm.) above the cardia. They were in close contact with each other and so formed a "collar" around the lumen of the terminal part of the oesophagus. At the cardia they joined the veins in the stomach wall and, cranially, they had numerous connexions with the submucous veins of the oesophagus. These subepithelial veins ranged in diameter from 1.5 to 2 mm., and the largest of them appeared to have been the site of recent haemorrhage.

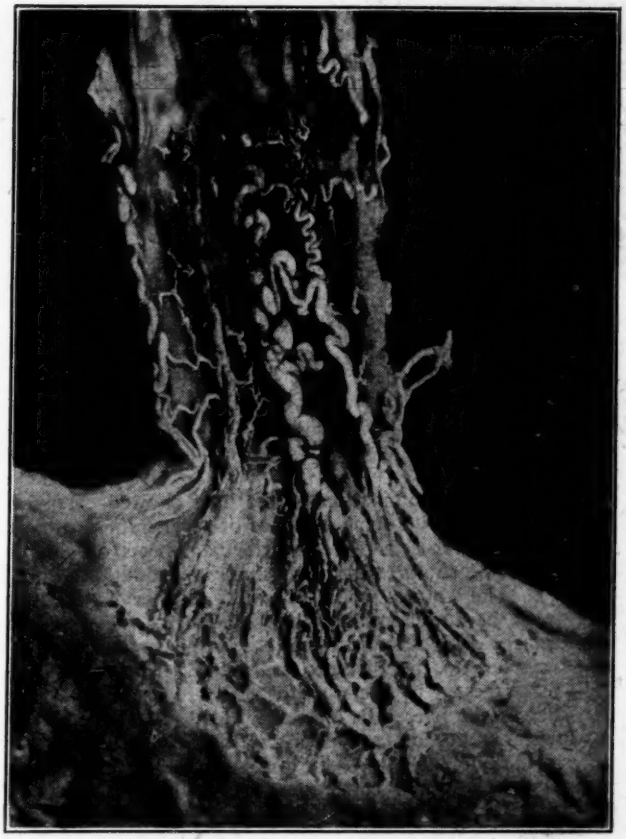

FIG. A.—Inner aspect of the oesophagus and stomach showing the size and extent of the varices. They have been injected with neoprene latex and exposed by removing the mucous membrane.

Four tortuous longitudinal veins, ranging from 2 to 4 mm. in diameter, were found in the submucosa. Normally, the longitudinal veins in the submucosa of the oesophagus are only a little over 1 mm. in diameter. These veins began at the cardia, and the largest of them could be traced as far as the level of the aortic arch. Many dilated and tortuous cross-anastomoses connected these veins. They received many tributaries from the dilated subepithelial veins and drained into dilated and tortuous veins upon the outer surface of the oesophagus. These veins accompanied the vagus nerves and had many connexions with the azygos veins, and caudally they joined the oesophageal tributaries of the left gastric vein. The latter vein and its tributaries were also dilated and tortuous.

There was a large vein in the free border of the falciform ligament which connected the left branch of the portal vein to the dilated deep epigastric vein. At its beginning this vein appeared to be a direct continuation of the left branch of the portal vein. It had an internal diameter of 6.2 mm. and its wall was 1.2 mm. thick. At a point 5.5 cm. from the last intrahepatic branch of the left branch of the portal vein the wall became abruptly reduced to 0.6 mm. thick. Here the hepatic end of the ligamentum teres merged into the thick-walled portion of the vein, suggesting that this part of the anastomotic vein was the hepatic end of the intra-abdominal part of the umbilical vein. This was confirmed by microscopical examination of the structure of its wall. The thin-walled portion continued alongside the ligamentum teres, and as it approached the abdominal wall it divided into two branches which were 3 and 4 mm. internal diameter. The smaller vein pierced the posterior wall of the rectus sheath cranial to the umbilicus; the larger vein pierced it caudal to the umbilicus. Both veins joined the tortuous and dilated deep epigastric veins and so drained into the caval system via the external iliac veins.

At the bare area of the liver and where the duodenum and colon were retroperitoneal were many conspicuous veins of Retzius. There were no piles.

There was considerable oedema of the retroperitoneal tissue but none elsewhere. The peritoneal cavity contained between 150 and 200 ml. of yellow fluid. The firm spleen was enlarged (390 g.) and had a dark purple cut surface showing an increase in the fibrous trabeculae and scattered purplish areas.

Microscopical examination of the liver showed extensive reticular fibrosis with some evidence of regeneration, though most of the liver cells were in irregular sheets or clumps and not in the characteristic "regeneration nodules" (Plate, Fig. 1). The clumps of regenerating liver cells did not appear to be stretching or distorting the stroma, and the appearances did not suggest that the portal venous obstruction was due to the pressure exerted by the regenerating cells as suggested by the work of Kelty *et al.* (1950). The majority of the liver cells appeared healthy, and the almost complete absence of fat was a striking feature. Proliferation of the bile ducts was seen in some parts of the sections. There were scattered collections of lymphocytes, often in association with proliferating bile ducts or areas of active fibroblastic proliferation. "Villi" of fibrous tissue, clothed with serosal cells, sprang from the surface of the liver.

The macroscopic and microscopical appearances of the liver were consistent with the conclusion that the "cirrhosis" was the late result of infective hepatitis.

Discussion

The outstanding feature of this case was the occurrence of a severe haemorrhage despite the presence of an unusually large anastomotic vein in the falciform ligament in addition to the more usual anastomoses in and around the oesophagus. Furthermore, this anastomotic vein was of the same order of size as the artificial anastomosis made by the surgeon between the splenic and left renal veins. The immediate cause of the haemorrhage appears to have been trauma of the oesophageal epithelium by the pieces of raw apple and erosion of one of the thin-walled subepithelial varices. Erosion and ulceration of the oesophageal epithelium is common in cases of oesophageal varices (Preble, 1900; McIndoe, 1928; Kegaries, 1934).

Learmonth (1949) and Snell (1950) have expressed doubts about the effectiveness of surgically produced anastomoses in reducing the risk of haematemesis from oesophageal varices. The case described by Learmonth (1949) showed a natural anastomosis, 6 mm. in internal diameter, between the splenic and left renal veins. The patient died of recurrent haematemesis. Cases of cirrhosis of the liver with a large anastomotic vein in the falciform ligament have been described under the name of "Cruveilhier–Baumgarten syndrome" (Armstrong *et al.*, 1942). Nearly all these cases showed haematemesis, and it was fatal in a large number. We have recently seen such a case in which the vein in the falciform ligament measured 13 by 4 mm. This patient had a small haematemesis which was apparently due to the erosion of a thin-walled subepithelial varix. Death was due to barbiturate poisoning, but it is possible that the patient would have had further bleeding had she lived longer.

It is reasonable to suppose that such naturally occurring anastomoses develop early in the evolution of the disease and that they increase *pari passu* with the increase in portal venous pressure. Should this be the case, they ought to be more effective in preventing the onset of haematemesis than the surgically produced anastomoses, which are in most cases not performed until bleeding occurs.

The routes whereby portal venous blood is by-passed into the caval veins may be divided into:

1. *Protected Routes.*—The veins upon the outer surface of the oesophagus, the veins of Retzius, the veins found in the falciform ligament, and the surgical anastomoses. These by-passes are not exposed to erosion and will reduce the risk of bleeding in so far as they reduce the pressure of the portal venous blood.

2. *Vulnerable Routes.*—The submucous veins and, more particularly, the thin-walled subepithelial veins of the stomach and oesophagus. By virtue of their position these veins are constantly exposed to trauma, and the risk of erosion will be increased by the distension of these veins by the high pressure of the portal venous blood.

These facts suggest that bleeding from oesophageal varices is due to two main factors: (1) The overdistension of the exposed thin-walled veins in the lamina propria and the submucosa by the high pressure in the portal vein. (2) Many of the dilated thin-walled veins are separated from the lumen of the oesophagus only by the epithelium, which is 0.2 mm. thick and may well be reduced by the stretching due to the underlying varices. Often there is erosion or ulceration of the epithelium over the varices. This seems to be due to trauma from food particles.

A large "protected" portal-caval shunt, whether naturally or artificially produced, will reduce the risk of bleeding only by reducing the size of the varices. Unless the "vulnerable routes" are removed or obliterated the progressive changes in the liver, with subsequent increase of portal venous pressure, will once more lead to the formation of distended varices. The case described above had reached the stage where the large natural shunt was no longer able to reduce the risk of erosion of the subepithelial varices. Therefore it is suggested that a large portal-caval shunt alone is not sufficient to prevent bleeding and that it should be combined with some measure to remove or obliterate the "vulnerable varices." It is also necessary to insist that patients with oesophageal varices should swallow only bland foods or purées in order to lessen the risk of erosion of the epithelium.

Summary

Fatal haematemesis in a case of oesophageal varices with an unusually large portal-caval anastomosis in the falciform ligament is described.

The anastomoses which develop between the portal and caval veins may be classified as either protected or vulnerable.

It is suggested that the formation of an artificial portal-caval anastomosis alone will not suffice to prevent bleeding, and it should be combined with measures to remove or obliterate the vulnerable varices in the lamina propria and the submucosa.

We wish to thank Dr. Leslie Cole for permission to publish this case, Professor H. A. Harris and Dr. A. M. Barrett for their advice and encouragement, and Mr. J. A. F. Fozzard and Mr. H. P. Hudson for the photographs.

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AUREOMYCIN: ITS TOPICAL USE IN SOME SKIN DISEASES

A CLINICAL STUDY

BY

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A very high percentage of cases met with in dermatological clinics in Dublin are pyogenic infections. The patients are slow to attend for treatment of such conditions, and the lesions are generally fairly extensive by the time they do so. A potent, non-toxic, easily applicable drug is therefore the ideal form of treatment, and "aureomycin" appears to fulfil these requirements. Aureomycin ointment (A.O.) is dispensed by Lederle Laboratories Division (1950) as a 3% aureomycin hydrochloride ointment in a petrolatum and wool-fat base.

The dermatologist has to contend principally with *Staphylococcus pyogenes aureus, Streptococcus haemolyticus, Proteus vulgaris,* and *Pseudomonas pyocyanea,* and aureomycin *in vitro* has shown itself capable of dealing with these organisms. It is shown in this paper that aureomycin is also effective *in vivo* when employed in ointment form.

Toxicity

The most important factor regarding the local use of an antibiotic is knowledge of its sensitizing potentialities. Experience with the disadvantages of sulphonamides and penicillin is well known. Siegel and Schantz (1950) obtained data in the case of aureomycin by using the "prophetic patch test" method of Schwartz and Peck (1946) on 127 subjects, including doctors and nurses, but obtained no positive reactions. This test is far from infallible, because it is used on healthy skin, but it does give some idea of the sensitization index of the drug.

Sensitivity has, however, been noted by Siegel and Schantz (1950), Hollander and Hardy (1950), and a few other authors in a small percentage of cases. Reactions were perhaps to be anticipated, as they occurred in patients already suffering from an allergic skin disease, notably atopic dermatitis. Of the 12 cases of this condition which are described below, two showed local sensitivity.

At the beginning of this trial of A.O., only pyogenic infections were treated, but a miscellaneous group of conditions was included towards the end. None of the patients was admitted, which made the test a severe one, as it was impossible to tell whether the instructions were being properly carried out.

No tabled control is included in this series. The number of cases in the various groups was too small and the sum of variables too many to permit of a statistical analysis. The only series in which two different applications were employed at the same time is described in the case of warts. Results were assessed by clinical appearances. The following groups were treated: sycosis barbae, 22 cases; folliculitis of other areas, 12; impetigo, 57; miscellaneous group, 53.

Sycosis Barbae

This aggravating condition responded well to A.O. (see Table I). Some of the cases were of very long duration, and many had previously received numerous different forms of treatment. The ointment was applied thinly and gently to the affected areas twice a day, which included once after shaving. Within a week improvement was noted in all cases, and in four mild cases cure resulted. In all other cases, excluding Nos. 1, 2, and 8, the pustules had disappeared by the end of a fortnight. In these three cases occasional pustules remained until

TABLE I.—*Sycosis Barbae*

Case No.	Duration of Disease	Clinical Type	Bacteriology	Previous Treatment	Treatment Time	Follow-up
1	5 years	Severe	Pen.-sen. S.P.A.	Pen.; Quin.; *X* rays; Sulph.	6 weeks	7 months
2	1 year	,,	Pen.-sen. S.P.A.	Pen.; Quin.; *X* rays	5 ,,	7 ,,
3	6 months	Mod.	S.P.A.	Pen.; Quin.; Vio.	3 ,,	6 ,,
4	3 weeks	Mild	S.P.A.	Nil	2 ,,	4 ,,
5	2 ,,	,,	—	,,	1 week	18 weeks
6	3 months	,,	S.P.A.	Sulph.; Pen.	3 weeks	5 months
7	8 ,,	Mod.	Pen.-sen. S.P.A.	Pen.; Vio.	3 ,,	5 ,,
8	2 years	Severe	S.P.A.	Pen.; Sulph.; Ung. S. and S.; Vio.	5 ,,	7 ,,
9	15 months	,,	S.P.A.	Pen.; Quin.; *X* rays	5 ,,	6 ,,
10	2 weeks	Mild	—	Nil	1 week	4 ,,
11	4 ,,	,,	—	,,	2 weeks	18 weeks
12	2 months	,,	S.P.A.	Ung. S. and S.	2 ,,	18 ,,
13	10 ,,	Mod.	,,	Fen.; Sulph.; *X* rays; Vio.	4 ,,	7 months
14	9 ,,	Severe	,,	Pen.; Vio.; *X* rays	5 ,,	6 ,,
15	6 weeks	Mild	—	Quin.	2 ,,	4 ,,
16	18 months	Severe	S.P.A.	Pen.; Quin.; *X* rays	5 ,,	6 ,,
17	3 ,,	Mod.	—	Pen.; Quin.; Vio.; Arg.	2 ,,	4 ,,
18	11 ,,	,,	—	Quin.; Arg.; Pen. (loc. and syst.); Ung. S. and S.	2 ,,	5 ,,
19	9 years	Severe	—	*X* rays; Quin.; Staph. vac.	4 ,,	14 weeks
20	3 months	Mild	—	Quin.; Vio.; Pen.	1 week	4 ,,
21	6 weeks	,,	—	Sulph. and Pen. (syst.); Ung. Bor.	1 ,,	4 ,,
22	8 ,,	Mod.	S.P.A.	Quin.; Pen.	3 weeks	6 months

Pen.-sen. = Penicillin sensitive. Pen. = Penicillin preparation. Vio. = Vioform. Sulph. = Sulphonamide preparation. Ung. S. and S. = Ung. sulphur and salicylic acid *B.P.* Quin. = Ung. quinolor Co. S.P.A. = *Staphylococcus pyogenes aureus.* Staph. vac. = Mixed staphylococcal vaccine. Arg. = Argyrol.

the end of the third week. On account of this manifestation, treatment was maintained for prophylactic purposes for several weeks after resolution of the lesions, though further experience will probably deem this precaution to be unnecessary.

All patients returned for regular examinations, and no relapse has yet occurred. No case, fortunately, was resistant to A.O.

Folliculitis of Other Areas

Details of the 12 cases treated are shown in Table II. Case 3 showed some improvement after six weeks' treatment, but a small number of lesions remain. It has been the only resistant case of folliculitis. Previous treatment in Tables I and II indicates treatment which

TABLE II.—*Folliculitis of Other Areas*

Case No.	Duration of Disease	Area	Clinical Type	Bact.	Previous Treatment	Treatment Time
1	6 weeks	Scalp	Severe	S.P.A.	Ung. S. and S.	2 weeks
2	2 ,,	Arms	Mild	,,	Nil	7 days
3	15 months	Legs	Severe	,,	Pen.; Sulph.; Vio.; Ung. S. and S.	(See text)
4	3 weeks	Thighs	Mild		Nil	7 days
5	6 ,,	Groin; axilla	Mod.	S.P.A.	Pen. (loc. and syst.)	3 weeks
6	10 days	Scalp	Mild	—	Nil	7 days
7	2 weeks	Neck	,,	—	Ung. S. and S.	7 ,,
8	4 ,,	Chest; axilla	Mod.	S.P.A.	Sulph.; Vio.	2 weeks
9	8 months	Thighs; legs	Severe	,,	Pen. (loc. and syst.); Sulph.	2 ,,
10	10 ,,	Arms; legs	,,	—	Ung. S. and S.; Sulph. (syst.)	3 ,,
11	4 weeks	Scalp	,,	S.P.A.	Quin.; Ung. S. and S.	2 ,,
12	10 days	Leg	Mild	—	Nil	7 days

the patient has generally obtained outside hospital. I have not used sulphonamide or penicillin cream, on account of their unreliability as therapeutic agents.

It is worth noting here that Siegel and Schantz (1950) recommend 3% aureomycin hydrochloride in talc, as opposed to ointment, for use in folliculitis of the groin area.

Impetigo

Although I have previously found it more satisfactory to treat these cases with lotions than with ointments, A.O. has proved to be an exception. It is as speedy as penicillin in bringing about resolution without ill effects. The crusts were removed with boric soaks before applying the ointment.

Secondary impetigo in children attending the hospital is ten times as common as the primary variety, and is invariably secondary to pediculosis capitis, a disease which is rampant among the poorer classes. A.O. has been most effective in both varieties (see Table III). Most patients stated that a cure had occurred within four to seven days.

TABLE III.—*Impetigo*

Type	No. Treated	Cured	Aggravated
Contagiosa	12	12	—
Secondary to pediculosis capitis..	33	33	—
Secondary to atopic dermatitis ..	12	10	2

All cases of impetigo contagiosa showed *Staph. pyogenes aureus*, and five were also associated with a few colonies of *Str. haemolyticus*. Only twelve cases of the secondary variety had bacteriological examinations, which showed *Staph. pyogenes aureus*. The third group in this series consisted of nine cases of infantile eczema and three of atopic dermatitis. All except three of the babies had a family history of eczema, asthma, or hay-fever. The patients in the second group were all males, aged 18, 19, and 52, and gave histories of asthma. The cases which were aggravated by A.O. were the young men, who reacted acutely to the ointment. This sensitivity has already been mentioned.

Miscellaneous Group

Gravitational Ulcer.—Patients with varicose veins rarely attend hospital before ulceration has set in, and the ulcers are large, heavily infected, and emit a powerful and foul odour. Any treatment improving these conditions is to be recommended. A.O., by dealing with the infection, greatly accelerates the epithelization of the ulcer's edges. Local treatment of this condition differs. Oldham (1951), for instance, states that preliminary cleansing of the ulcer is unnecessary, no matter how foul, deep, or long-standing it may be, and that there is nothing to be gained by the application of antiseptics or antibiotics, because of the danger of aggravating the condition. Foote (1949), on the other hand, believes that in some cases hot fomentations or eusol dressings may hasten recovery. None of the 12 cases treated with A.O. showed skin sensitivity. An old technique was employed for application. The ulcer was dried after being cleaned with normal saline; a piece of gauze impregnated with A.O. was applied to the ulcerated area and covered with a pad of cotton-wool, which was held in position during the application of four Unna-paste bandages. Then a window was cut around the pad and a gauze bandage wound very firmly round the area. The pad was removed for daily dressing. In three cases the predominant organism was *Ps. pyocanea*, whilst in the remainder it was *Pr. vulgaris*. The response to A.O. was good in all cases; the floor of the ulcer was practically dry in 10–14 days, though organisms could still be cultured. Treatment was continued until the ulcer was healed. It cannot be claimed that aureomycin heals gravitational ulcers, but it greatly assists the other measures employed.

Acne Vulgaris.—Eight cases of the pustular type treated solely with A.O. did not show any improvement after eight weeks. Philip (1950) found, however, that the pustules cleared, but that the acne vulgaris was unaffected.

Acne Necrotica.—Three cases of this condition responded well to A.O. It was applied twice daily for six weeks. Within two weeks of suspension of treatment, however, varioliform lesions reappeared.

Chronic Paronychia.—Three cases of this condition of over six months' duration, which had been treated with various proprietary ointments, lotions, and penicillin cream, showed little improvement with A.O. after eight weeks' treatment. The failure may have been due to the patient's inability to introduce the ointment far enough beneath the bolstered nail-fold. Treatment might be successful if an aqueous solution of the drug was employed, thus ensuring deeper penetration.

Herpes Zoster.—Four cases of children with impetiginized lesions resolved within a week. The treatment did not appear to improve any other features of this condition.

Post-auricular Dermatitis.—Eight cases were treated They were all associated with seborrhoeic dermatitis

After 10–14 days resolution was complete. Culture showed that the organisms responsible in these cases were *Staph. pyogenes aureus* complicated by a few colonies of *Str. haemolyticus.*

Pustular Psoriasis.—The one case treated showed no response after six weeks' treatment.

Verruca Vulgaris.—Twelve cases were treated. The patients were instructed to apply A.O. to the warts on one side of the body, and an ointment containing only yellow paraffin to the other side. In three of the patients all warts had disappeared at the end of a month.

Verruca Plana.—Two cases were treated as for verruca vulgaris. One cleared in four weeks, the other still showed lesions after ten weeks.

Conclusions

There is no doubt that aureomycin ointment is a powerful addition to the therapy of pyogenic skin conditions. Its local sensitizing powers are low, contact dermatitis being produced in only two cases of this series, and they already had a history of allergy. The most striking performance was the rapidity with which cases, and especially the chronic ones, of sycosis barbae resolved. The temperamental nature of this condition is well known, and, although it may be said that the follow-up periods have not been long enough to pronounce a cure, the patients unanimously acclaimed the treatment as the best they had ever used.

Its efficacy in other pyogenic affections is equal to penicillin. One cannot hope to clear up completely a condition such as impetigo in less than four to seven days. Its great advantage over penicillin cream or ointment lies in the absence of untoward reactions. In the miscellaneous group it was most effective in acne necrotica, but, as with previous forms of local treatment, relapse soon occurred.

At the moment it would seem that aureomycin is the best available antibiotic in ointment form for pyogenic infections. Future use, however, may prove it less reliable; resistant strains of organisms and different examples of sensitivity may be encountered.

Summary

A clinical evaluation of 3% aureomycin hydrochloride ointment made in the treatment of 144 dermatological cases is described.

Sensitization in cases with past or present histories of allergy is described.

The ointment is simple to apply, and is stable over a long period without refrigeration.

I wish to thank Lederle Laboratories for providing me with supplies of the ointment, and in particular their representative in Dublin, Mr. M. Collins. I am also grateful to Dr. J. Martin Beare, of Belfast, for providing me with his results in five cases of sycosis barbae, which are included in Table I.

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TREATMENT OF GONORRHOEA WITH TERRAMYCIN

BY

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"Terramycin," prepared from the *Streptomyces rimosus,* is manufactured in golden 250-mg. capsules for oral use. It is of considerable value in urethritis, both gonococcal and non-gonococcal. Willcox and Findlay (1951) had 19 apparent clinical cures out of 20 male cases of non-specific urethritis treated with 6–12 g. of terramycin given over five to seven days; inclusion bodies were noted to disappear from the scrapings of the 14 male and 6 other female cases in which they were found.

The fact that terramycin is also effective against the gonococcus makes it a useful drug for the routine treatment of urethritis, be it gonococcal, bacterial, or viral in nature. Gocke *et al.* (1950) tested 28 strains of gonococci and found that this antibiotic ranked with "aureomycin" next to penicillin in effectiveness. Certainly it gives good results with gonorrhoea in the doses usually given for non-specific urethritis. For example, Caldwell *et al.* (1950) successfully treated seven patients on a 4–5-day regime.

However, all new drugs used for the treatment of gonorrhoea have to compete in effectiveness, in freedom from toxicity, and in ease of administration with single-injection methods employing penicillin. Hence early trials with terramycin have concentrated on simplicity of administration. Robinson (1950) had no fewer than three failures in six patients treated with single doses of 1 g. of terramycin, and 4 failures in 18 given a single dose of 2 g. As 3 of the latter 18 cases suffered from vomiting it was thought that single-dose techniques were not likely to prove as successful as previously tried methods. These difficulties were to some extent avoided by Hendricks *et al.* (1950) by giving two doses at an interval of six hours. Cures were noted in all of 15 cases given two doses of 1 g., and in 8 of 10 cases given two doses of 500 mg.

Single- and double-dose methods have been employed in the present study, but the results obtained, though successful, have not been quite as striking as those of the American series.

Twenty-nine cases of gonorrhoea have so far been treated at St. Mary's Hospital, London, and at King Edward VII Hospital, Windsor. Twenty-six were males and three were females, the average age being 28.8 (extremes 20–44 years). Five were treated with but a single dose, 23 by two doses, and the only one complicated case, a man with epididymitis, by multiple doses (see Table).

Summary of All Methods

Method	Treated	Observed	Relapse Gc +	Non-specific Infection	Reinfection	Proved Failure Rate %
Single dose, 1 g.	1*	1	1	—	—	—
,, ,, 2 g.	5	5	2	—	—	40·0
Double ,, 2 g.	23	19	2	2	1	10·5
Multiple ,, 5 g.	1	1	—	—	—	—
Total ..	30	26	5	2	1	19·2

* This case is also included among the five cases that received a single dose of 2 g.

Single Dose (5 Cases)

Four were male and one was female, all with uncomplicated gonorrhoea. One patient, given only 1 g. of terramycin, responded initially but relapsed three days later and gonococci were again found in the urethral smear on the fifth day. He was then treated with a single dose of 2 g., but the condition relapsed a second time seven days later, when he was given penicillin. Of four others given single doses of 2 g. one relapsed at nine days and was given penicillin. The remaining three, so far observed for 28, 125, and 138 days, respectively, have shown repeatedly normal urethral and prostatic smears and cultures and serological tests. The two patients who have been observed for 28 and 138 days are husband and wife, and both have remained well in spite of regular bi-weekly sexual intercourse together over a period exceeding three months.

Double Doses (23 Cases)

Twenty-one males and two females, all with uncomplicated gonorrhoea, have been treated with two doses of terramycin, each of 1 g., given orally six hours apart. Four patients defaulted at once. The remaining 19 have been observed for periods varying from less than two weeks in 4 to from 14 to 75 days in 15.

There were two definite failures, each showing a urethral discharge containing gonococci five days after treatment. One of these responded to re-treatment with terramycin given as 500 mg. twice daily for two days, and the other, a lorry driver, was re-treated with penicillin but suffered two subsequent "relapses" within a very short time. Another patient, a Nigerian Negro, was thought to have a reinfection. One week later he was found to have a urethral discharge containing gonococci, but he admitted to having had sexual intercourse with the girl from whom he caught the infection during the evening of the day he had received the first dose. He was again treated with terramycin, this time successfully.

Two other patients, later found to possess urethral discharges not containing gonococci, were re-treated for non-specific infections. Some persons may regard these cases as having been incompletely cured gonorrhoea, but most will regard them as being either due to the effect of secondary organisms upon tissues traumatized by the departed gonococcus or as concomitant infections of non-specific urethritis. One of these patients was again treated, 14 days after the first treatment, with two further doses of 1 g. of terramycin. After observation extending over 63 days he was quite free from urethral discharge during the day, and his urine was clear, but a morning gleet which contained a few pus cells per field persisted. In the other patient pus cells but no gonococci were seen in the urethral smear taken on the eighth day. He was then given 250 mg. of terramycin four times daily for four days. One week later he still complained of an early morning gleet and threads were observed in his urine, but unfortunately he did not attend again. The remaining 14 patients were well, and repeated urethral and prostatic smears and cultures were negative throughout observations extending from 1 to 75 days.

Multiple Doses (1 Case)

One man, aged 31, had gonococcal urethritis complicated by a well-marked unilateral epididymitis. He received 1 g. of terramycin in a single oral dose initially and this was followed by 250 mg. given four times a day for four days. Relief from pain was immediate and the swelling quickly subsided. His progress has been entirely satisfactory during 29 days of post-treatment observation. Moreover, his wife was also found to have a severe gonococcal urethritis and cervicitis. She was treated with terramycin by the double-dose method, and she too has shown repeatedly negative smears and cultures over the same time.

Discussion

Side-effects.—The side-effects produced by the small doses of terramycin given were minimal. One patient admitted to heartburn, and two to "soreness of the back passage," a complaint noted more often in the larger series of non-specific urethritis cases for which bigger doses were employed. On the other hand, one man who was suffering from coryza at the time of treatment enthusiastically declared at his next visit that the terramycin had cured it, and, indeed, asked for some more when another cold developed later.

Masking of Syphilis.—Like penicillin, terramycin has a definite action upon syphilis. Spirochaetes were banished from the lesions of six cases of early syphilis and sero-reversal was obtained in two cases reported by Hendricks *et al.* (1950). Likewise, Schoch and Alexander (1950) noted healing in two cases. Similarly, Loughlin and Joseph (1951), in a large-scale study of 150 cases of yaws in Haiti, noted most dramatic initial results when 7–10 g. of terramycin was given over three to five days.

It was considered interesting to note the effect of the double-dose method on a case of well-marked secondary syphilis.

Case Report

The patient was a female domestic servant aged 25. She had generalized glandular enlargement, typical inguinal adenitis, multiple ano-genital condylomata in specimens from which numerous *Treponema pallidum* were seen under the dark field, mucous patches in the mouth, and bald patches on the tongue, but *no* rash. The serum Wassermann and Kahn reactions were both strongly positive. She was given two doses of terramycin, each of 1 g., at an interval of six hours, in the manner adopted for the treatment of gonorrhoea. She was then observed for 24 hours before beginning intensive therapy with penicillin.

The first dose of 1 g. was given at 6 p.m. When seen at 11 p.m. there had been no pyrexial response and a second dose was ordered to be given at midnight. By the time that she had received it, however, her temperature had already risen to 99.4° F. (37.4° C.) and her pulse, which had been 80 or below, to 88. By 2 a.m. the temperature was 100° F. (37.8° C.) and the pulse rate showed a steep rise to 106. At 4 a.m. the pulse had fallen again but the temperature was 100.4° F. (38° C.). Her temperature fell to 99.8° F. (37.7° C.) by the following morning.

The patient was examined at noon (18 hours after receiving the first dose) and there was then noted an obvious roseolar rash which had not been evident the night before. A dark-field examination of serum squeezed from the condylomata revealed numerous vigorously motile spirochaetes. A further dark-field examination was performed at 6 p.m. (24 hours after the first dose of terramycin) and again spirochaetes were found without much difficulty, but by this time they were somewhat reduced in number and markedly sluggish in their movements. She was then given the first of eight daily injections of 600,000 units of procaine penicillin G with 2% aluminium monostearate, and it is interesting to observe that

no further Herxheimer reaction was noted and that the temperature remained normal and the pulse at 80 or below.

As two doses of terramycin, each of 1 g., at an interval of six hours exerted such a definite effect in established secondary syphilis, and as it is probable that larger doses and/or longer periods of treatment are necessary properly to cure gonorrhoea with this drug, it appears that terramycin does not differ from penicillin in its capabilities in masking undeclared syphilis for which smaller doses than those given would be sufficient.

Summary and Conclusions

Three of six treatments of acute gonorrhoea with single doses of 1–2 g. of terramycin given orally were unsuccessful. However, only two relapses (10.5%) were noted in the 19 cases followed up out of the 23 that were given two oral doses each of 1 g. spaced six hours apart, although there was one reinfection and two others were treated for non-specific infections.

Two doses of 1 g. of terramycin at an interval of six hours were given to a girl with secondary syphilis. A febrile Herxheimer reaction resulted, with the appearance of a previously unseen roseolar rash. Eighteen hours after the first dose the dark field contained an abundance of motile spirochaetes, but at 24 hours they were very sluggish in their movements. The patient was then treated with daily penicillin and no further Herxheimer reaction was observed.

Terramycin is thus clearly effective against gonorrhoea. In the small series described it was not quite as effective as penicillin at its best, though the results were better than those of King *et al.* (1950), who, by including all cases of secondary urethritis and reinfection as failures, showed penicillin at its worst; and more prolonged schedules with terramycin remain to be tried.

Even if terramycin does not replace penicillin in the treatment of gonorrhoea it is likely to have a considerable application for persons who dislike injections, for those who are unable to obtain injections without difficulty (ship's crews, etc.), for cases of gonorrhoea which are resistant to penicillin if and when they arise, and as "an emergency kit" for both treatment and prophylaxis of the traveller and the soldier. Like penicillin, however, it may mask undeclared syphilis.

Grateful acknowledgments are due to Messrs. Chas. Pfizer and Co. Inc., of New York, for so generously supplying the terramycin used in this tudy.

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At the 13th International Congress of Military Medicine and Pharmacy held recently in Paris, Major-General E. E. Hume read a paper entitled "United Nations Medical Service in Korean Conflict" (*J. Amer. med. Ass.*, August 4, p. 1307). He remarked that Korea was about the size of Italy, with many mountains strikingly like the Apennines. The winter was the coldest in which American troops had fought, and in the first eight months of the campaign the United States Army sustained nearly five times as many casualties as in the American Revolution (1775–83), though the two world wars, and strangely enough the war of 1861–5 between North and South, all cost more lives.

Medical Memoranda

Clean Catheterization

The importance of aseptic atraumatic catheterization of the male urethra should not need emphasis, but observation shows that there is a common lack of knowledge of a suitable technique. The hasty insertion of a poorly lubricated catheter into a dirty meatus results in sepsis, which may be fatal, or failure to pass the instrument owing to the spasm which results. One problem is that of adequate lubrication and distension of the urethra. The injection into the urethra of a mixture of petroleum jelly and paraffin, which is often useful in passing small bougies through tight strictures, was thought undesirable, as there was a risk of introducing some of the mixture into the bladder, where it might form the nucleus of a stone. The usual water-soluble jellies have, in my opinion, very poor lubricating properties. The small amount of mercury oxycyanide contained in some of them is probably inefficient as an antiseptic and may act as an irritant.

A stiffer jelly containing a sulphonamide seemed desirable, and the help of the hospital pharmacist, Mr. B. W. Coultas, was sought. Mixtures of alginates or tragacanth with sulphathiazole or sulphacetamide were found unsatisfactory, and after many experiments a jelly of 3% "promulsin" with 5% sodium sulphacetamide was produced and found satisfactory. This can be sterilized in the autoclave, and is dispensed in rubber-capped glass tubes containing 15 ml. This formula was evolved at about the time Stewart's (1949) paper on prostatic obstruction was published, and it is evident that we were working along the same lines. In order to avoid introducing infection in acute or chronic retention of urine due to prostatic disease, many urge that the use of a catheter should be banned except as a prelude to immediate operation. This is the ideal, but there must be occasions when its use cannot be postponed or is desirable for some other reason—for example, in post-operative retention—and it is hoped that the following routine may lessen some of the dangers.

If pain is present a suitable analgesic—morphine, pethidine, or amidone—should be given, preferably intramuscularly. The following are required: 10-ml. glass "record" or urethral syringe with rubber tip; penile clamp; container for local analgesic; catheter, usually a soft rubber No. 10; one pair of artery forceps; solution of percaine 1 in 500 with 1 in 200,000 adrenaline; and antiseptic jelly. The pubic hair is cut short, and a thorough toilet with soap and water carried out. Percaine solution, 10 ml., is injected into the urethra and the penile clamp applied for three to five minutes. Meanwhile the syringe is filled with the promulsin jelly. As it is somewhat glutinous it is necessary to pour it into the open end of the syringe barrel. After milking as much as possible of the anaesthetic solution into the posterior urethra the remainder is allowed to escape. The catheter, clipped at the outlet with the artery forceps, is lubricated with the remainder of the jelly, taking care not to block the eye. The clipped end produces an air-lock as noted by Stewart. The jelly is then injected into the urethra, distending it moderately. It will be

found that the catheter glides in easily and painlessly with the minimum resistance at the external sphincter.

This technique may seem elaborate and time-consuming, but it must be borne in mind that the urethra is highly susceptible to infection, and minor sepsis may result in a long convalescence from a simple bladder operation or, at worst, an ascending renal infection. The time taken is well spent, as it diminishes the risk of failure, with its inevitable shattering of the morale of the patient.

EDRIC F. WILSON, F.R.C.S.,
Surgeon, South Devon and East Cornwall Hospital.

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A Modification of Millin's Retropubic Prostatectomy

The object of this communication is to bring forward a slight modification of Millin's retropubic prostatectomy, which simplifies the operation without, I think, detracting from the good results. In most cases it is not very difficult to incise the prostatic capsule transversely, but I have had a few difficult cases, such as adipose patients and those with low-lying prostates, prostates unduly close to the pubes, and bony bosses behind the symphysis.

In one case of adiposity I found I had made the incision through the junction of the bladder and the prostate into the bladder. An easy enucleation followed by a primary closure led to an excellent result. Since then in any case of difficulty I have done the same again, with satisfactory results.

Method

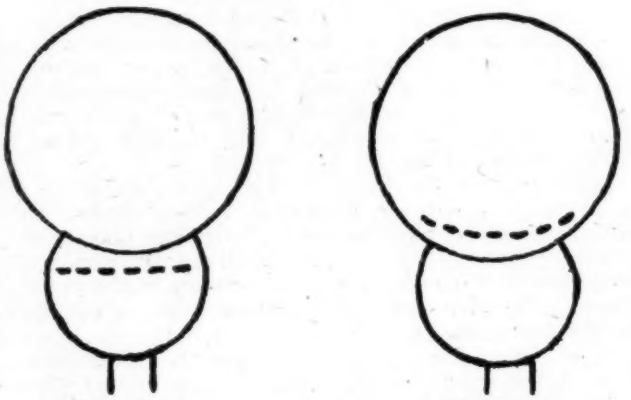
A catheter is passed and the bladder emptied. The table is put up in a 45-degrees Trendelenburg position and raised as high as it will go. A midline incision is made through the skin, fat, and linea alba from the pubes to within 1 in. (2.5 cm.) of the umbilicus—this incision is long, but makes possible a good exposure, and clean healing takes place. Retractors are put in and the retropubic space is opened up with the index finger, displaying the front of the bladder and the prostate. I have found the best source of illumination is a good spot-light adjusted by the anaesthetist.

Any visible veins on the front of the prostate and lower part of the bladder are carefully clamped and diathermy is applied. The bladder is then incised transversely immediately above the prostate, the length of the incision being just greater than the width of the prostate; any bleeding vessels in the incision are clamped and diathermy is applied. The inside of the bladder is inspected and palpated, using the bladder spreader as a retractor.

The table is then lowered and the prostate is enucleated digitally. The upper part of the bladder is retracted upwards and a wedge of the trigone is removed with curved scissors. Any bleeding points are clamped and treated by diathermy. A good light, good retraction, and a sucker are essential here. Oozing is stopped by plugging the prostatic cavity with gauze for five minutes. The catheter is pulled upwards and placed in the bladder, and the bladder incision is stitched up in two layers with continuous catgut. Penicillin powder is insufflated, a small rubber suprapubic drain is put in, and the wound is closed. The catheter is stitched to the foreskin or to the glans, 20 ml. of sodium citrate is put in the bladder with a syringe, and a spigot is placed in the end of the catheter.

When the patient is in bed the spigot is removed and the catheter connected up to a jar beneath the bed, the end of the tube being under water. Daily injections of "distaquaine" are given for a week, and 20 ml. of sodium citrate is put into the bladder six-hourly for the first 48 hours. The suprapubic rubber drain is removed in 24 hours and the catheter in 48 hours.

The patient is allowed out of bed any time after the first 48 hours. He is usually walking about in three or four days, and goes home, healed, at the end of the second week.



Millin's incision Modification

The centimetre difference in the position of these two incisions can make all the difference between an easy operation and a difficult one.

Comment

The advantages of the modification are: (1) it is easier to perform; (2) inspection and palpation of the bladder are simpler and more effective—this may do away with a preliminary cystoscopy and so save time; (3) it is quicker—this is important; (4) bleeding is rather less; and (5) absolutely accurate suturing of the bladder wall in two layers makes leakage unlikely.

The disadvantage of the modification is that it is perhaps a little more difficult to get absolute haemostasis, though it is probably correct to say that the urine is red during the first 24–48 hours whatever method is adopted. If every bleeding point is clamped, diathermy applied, and the prostatic cavity plugged for five minutes, haemostasis is adequate.

The following points are, I think, of importance and perhaps of interest: (1) the general practitioner should be encouraged not to catheterize the patient but to send him into hospital at once; (2) all except the moribund and grossly infected cases can be accepted for operation; (3) acute retention of urine due to prostatic enlargement is an emergency necessitating immediate prostatectomy; (4) with primary closure and clean healing the fear of prostatectomy can largely be dispelled, and we can hope to get more cases early; (5) the operation described is within the scope of the general surgeon, as distinct from the urological specialist.

ERIC COLDREY, M.D., F.R.C.S.

Reviews

OSLER

Selected Writings of Sir William Osler, July 12, 1849, to December 29, 1919. With an Introduction by G. L. Keynes, M.D., F.R.C.S. (Pp. 278. 15s.) London: Geoffrey Cumberlege (Oxford University Press). 1951.

It is a sad reflection that specialism in medicine inevitably demands so much effort and concentration that it leaves its exponents little time to wander amid the woods of Academus or to pursue the study of the humanities. Nor with the advances of the art and science of medicine can one man to-day take the whole realm of medicine for his own and write an authoritative textbook, as Osler did, which will always remain "a pattern of style in medical writing."

Sir William Osler succeeded in his day not only in being a "physician of two continents," a famous clinical teacher, and an inspirer of medical research and of organizations for conquering disease, but also in achieving distinction as a man of letters. Professor Welch said that not since Linacre had there been a more distinguished classical scholar among physicians; and, referring to Osler's presidency of the British Classical Association in 1919, he wrote:

"It was in recognition not merely of his sympathetic interest in classical studies and intimate association with classical scholars, but also of his mastery of certain phases of the subject, especially the bibliographical and historical sides, and the relation of the work and thought of classical antiquity to the development of medicine, science, and culture."*

As a centenary tribute to their patron saint, a committee of the Osler Club of London, with the help of Dr. W. W. Francis, have selected sixteen of Osler's addresses and essays to illustrate the sweep of his mind and interests, which embraced so many phases of human activity. This well-printed book, with five illustrations, has been ably edited by Dr. A. White Franklin, and is adorned by an introduction from G. L. Keynes which includes a sketch of Osler's life and work.

To the diminishing band of those who knew Osler the reading of these essays will recall many memories of that delightful personality and of the bibliographical lore which he was ever ready to expound to the questing student. To those, whether doctors or laymen, who meet Osler as a humanist for the first time in these pages new paths of thought will open, and they will be enriched by a wise and helpful philosophy to meet the vicissitudes of life.

The selection could hardly have been bettered. First come the oft-quoted remarks on "Creators, Transmuters, and Transmitters." The address on "The Old Humanities and the New Science," delivered to the Classical Association, deplores the latter-day separation between philosophy and humane letters and science, children of the same mother, brought into the world by the Greeks. Included also is the address on "Sir Thomas Browne," Osler's first love and his last, whose favourite edition lay on his bier in Christ Church Cathedral. We meet the "fantastic great old man," Robert Burton; Michael Servetus, the martyr of science; Gui Patin; and "The Young Laennec"; and learn from Osler how to live "the student life," about "teaching and thinking," "the growth of truth" (his Harveian Oration), and "a way of life." The bibliophile is instructed in the entomology of the insect bookworms, about "books and men," and the "collecting of a library." The doctor will like the story of William Beaumont, showing how a gunshot wound which produced a gastric fistula in a patient enabled a United States army surgeon in the backwoods of America to make fundamental observations on the physiology of the gastric juice and digestive processes; and Osler's letters to his house-physicians give a vivid picture of medical teaching in Germany and Switzerland in the 'nineties.

Here is the best of Osler the humanist. The committee of the Osler Club have produced a worthy memorial to the great physician, one which he himself would have esteemed.

ARTHUR S. MACNALTY.

*H. Cushing (1925): *The Life of Sir William Osler*, Vol. II, p. 650.

HANDBOOK ON ALLERGY

Pediatric Allergy. By Robert Chobot, M.D. (Pp. 284. £1 18s. 6d.) London: McGraw-Hill Publishing Co. 1951.

This small book has been written for the student taking a course in paediatric allergy and for paediatricians and general practitioners who wish to widen their knowledge of the subject. It is clearly written and well produced, and within the limits the author has set himself it fulfils its purpose well. The author treats the subject on the usual lines, with chapters on diagnostic procedures, asthma, hay-fever, vasomotor rhinitis, eczema, migraine, and other subjects. There are special chapters on food and drug allergy, allergy of the eye, and physical allergy, and a short note on A.C.T.H. The book ends with 28 illustrative case histories. Controversial subjects are not discussed at length, and the book is a short practical approach to the subject by an obviously experienced paediatric allergist. It can be recommended warmly to the physicians to whom it is addressed.

C. J. C. BRITTON.

MEDICAL PROBLEMS IN THE TROPICS

Health and Disease in the Tropics. By Charles Wilcocks, M.D., F.R.C.P., D.T.M.&H. Illustrated by John Hill Grundy and the Author. (Pp. 200; 33 figures. 15s.) London: Geoffrey Cumberlege (Oxford University Press). 1950.

As the development of tropical countries and their resources continues at an increasing pace, and as the indigenous populations become ever more conscious of their own part in this development, it becomes increasingly necessary for all concerned to have some balanced and clear knowledge of the primary problems of life in the Tropics, of which those of health and disease are paramount. Dr. Wilcocks has written an admirable handbook which meets this need. Besides giving accurate and comprehensive yet concise and clear accounts of the more important tropical diseases, he particularly focuses attention on the application of this basic knowledge to the welfare of the peoples of the Tropics. The book is designed primarily for officers of the Colonial Administrative Service, managers of plantations or mines, and missionaries and others who, without specialized knowledge of tropical medicine, may come into contact with its problems.

The descriptions of the various diseases are well done and cover such matters as distribution, cause, transmission, symptoms, and prevention; while they are devoid of unnecessary detail, their accuracy and clarity have in no way been sacrificed In other equally admirable chapters the author discusses important general matters such as housing, water supplies, and sewage and refuse disposal. In the chapter on health policies and organization he particularly emphasizes the important part played by administrative officers, who, being the experts on matters of law and tribal custom, can usually assess better than most others the effect of any suggested activities on the minds of the people, and are most likely to be able to win over any suspicious or conservative population. Furthermore, most welfare activities in the Tropics involve several departments—for example, medical, agricultural, veterinary, and educational. The success of any scheme depends on good will and co-operation, and co-operation is more likely to be obtained if all concerned have had some opportunity of acquiring the appropriate background of knowledge. So far as tropical medicine and hygiene are concerned, no book could more concisely and clearly provide such a background than does Dr. Willcocks' work. It can with profit and pleasure be read by all—including doctors, nurses, and medical assistants—who have to deal with the health and welfare problems of tropical peoples, as well as by those for whom it is specifically designed.

F. MURGATROYD.

PHYSIOTHERAPY AND CHILD-BEARING

Physiotherapy in Obstetrics and Gynaecology. (Including Education for Childbirth.) By Helen Heardman, M.C.S.P. Forewords by W. C. W. Nixon, M.D., F.R.C.S., F.R.C.O.G., and Veronica Shand, S.R.N., S.C.M., M.T.D. (Pp. 228; illustrated. 16s.) Edinburgh: E. and S. Livingstone. 1951.

Mrs. Heardman was one of the leading practitioners and teachers of physiotherapy in relation to child-bearing, and it is fortunate that she was able to complete this record of her methods and experience before her recent tragic death in a street accident. It will be welcomed, not only by her own students, but by all those who intend to take up this particular type of work.

The book is written in simple language and is intended primarily for physiotherapists, but it should also prove of great value to all who practise midwifery, no matter whether they be doctor or nurse. It gives the answers to some of the awkward questions likely to be asked by the modern expectant mother—who has usually heard tell of mental and physical preparation for childbirth. It is mostly concerned with antenatal and postnatal exercises, and these are introduced by brief accounts of the anatomy and physiology of pregnancy, with occasional diversions into psychology and allied matters. The author discusses the preparation and management of the breasts for lactation; in a smaller section she considers physiotherapy for displacements and disease of the pelvic organs, and exercises after gynaecological operations.

The real attraction of this volume for the doctor lies in its detailed descriptions and illustrations of all the various exercises appropriate to different circumstances, for these are matters not to be found in most medical books.

T. N. A. JEFFCOATE.

PSYCHOLOGY OF CHILDREN

Jealousy in Children. By Edmund Ziman, M.D. A Guide for Parents. (Pp. 236. 12s. 6d.) London: Victor Gollancz. 1951.

This book is mostly descriptive. The author writes to inform parents about their children so that they may manage them along sensible lines. Instead of talking about emotional development as a whole, he has chosen this one theme, jealousy, and has built a book around it. He has plenty of case material, given in a simple way which parents can understand and which will enlarge their experience, and he is all the time sympathetic with parents and children.

The author has derived more than theoretical formulations from psycho-analysis. He has an appreciation of dynamic psychology, and thinks of the individual in terms of the continuity of emotional development. Nevertheless this book remains descriptive and suitable for parents. It therefore contains nothing that an informed psycho-analyst does not know about jealousy, and it avoids its deeper significances. Psychiatrists will read the book only in order to form an opinion on its suitability for being recommended to parents. I think they will want to recommend it.

D. W. WINNICOTT.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Headaches. By N. D. Fabricant, M.D. (Pp. 149 7s. 6d.) London: Staples Press. 1951.

The Retarded Child. By H. Loewy. (Pp. 160. 10s 6d.) London: Staples Press. 1951.

Early Embryology of the Chick. By Professor B. M. Patten. 4th ed. (Pp. 244. 27s. 6d.) London: H. K. Lewis. 1950.

St. Thomas's Reports. Vol. 6, second series. (Pp. 285. No price.) London: St. Thomas's Hospital. 1950

Skull Fractures and Brain Injuries. By H. E. Mock, M.D. (Pp. 806. 114s.) London: Baillière, Tindall and Cox. 1950.

Handbook of Psychology. By J. H. Ewen, F.R.C.P.Ed., D.P.M. (Pp. 215. 25s.) London: Sylviro Publications. 1950.

Chambers's Dictionary of Scientists. By A. V. Howard, B.Sc. (Pp. 250. 12s. 6d.) London: W. and R. Chambers. 1951.

Biology Staining Schedules. By R. R. Fowell, M.Sc. 4th ed. (Pp. 27. 2s 6d.) London: H. K. Lewis. 1951.

National Smoke Abatement Society Year Book 1951. (Pp. 44 1s.) London: National Smoke Abatement Society. 1951.

Prostitution and the Law. By T. E. James, M.A., B.C.L. (Pp. 160. 21s.) London: William Heinemann. 1951

The Chemist and Druggist Poisons Guide. Compiled by W. A. Whatmough, B.Sc., Ph.C., F.R.I.C. Vol. 1: Poisons Lists and Key. (Pp. 89. 20s.) London: The Chemist and Druggist. 1951.

My Six Convicts. By Donald Powell Wilson. (Pp. 336. 15s.) London: Hamish Hamilton. 1951.

Case Finding and Patient Management Through an Understanding of Known Syphilitic Patients. Issued by the Mississippi State Board of Health and Federal Security Agency Public Health Service. Vols. 1 and 2. (Pp. 378. No price.) Mississippi: Federal Security Agency. 1950.

Handbuch der inneren Medizin. Vol. 2. *Blut und Blutkrankheiten.* By Dr. L. Heilmeyer and Dr. H. Begemann. 4th ed. (Pp. 1,179. M. 198.) Berlin: Springer-Verlag. 1951.

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STUDIES OF UNDERNUTRITION

It was concluded at the Hot Springs Conference in June, 1943, that "the first cause of hunger and malnutrition is poverty." Severe famines, however, are usually caused by failure of crops, as in Ireland in 1846, India in 1899–1900, and the Ukraine in 1933. In such cases the urgent necessity of famine relief usually precludes the scientific study of the victims: little new information came from the Bengal famine. Similarly, severe food shortages caused by war can seldom be studied with scientific precision. During the first world war famine oedema appeared in Poland early in 1915 and rapidly became common among prisoners and displaced persons; a large number of papers were published upon this condition, but little was added to knowledge of its aetiology. After that war, Harriette Chick and her colleagues, sponsored jointly by the Medical Research Council and the Lister Institute, visited Vienna, where in September, 1919, famine oedema had been prevalent but was no longer so, and scurvy was common among infants only; rickets and "hunger-osteomalacia" were frequently present in people of all ages. Rickets they studied in detail during 1919 to 1922 in von Pirquet's wards, and their results were published in an important report.[1]

Some valuable studies were made during the Spanish Civil War, particularly on the nervous system.[2] During the second world war starvation appeared in many parts of the world, but usually in circumstances where facilities for scientific work were not available, as in the slavery of concentration camps, or when those with facilities were fully engaged on public health work. However, remarkable objective observations were made in the Warsaw Ghetto in 1941 and 1942,[3] and detailed studies were made, for instance, by Brull and Simonart in Belgium, and Gounelle and Trémolières, in France; these and other observations were briefly communicated to a symposium held at Liége in October, 1946, and the published volume, edited by Bigwood,[4] contains a great deal of useful information, much of which is unpublished elsewhere. The two severe famines for which most information is available were those in Greece between May, 1941, and April, 1943, and in Western Holland between September, 1944, and May, 1945. The Dutch famine was intensively studied immediately after the German capitulation. Relief teams were ready to move in: the Dutch under Burger, the American under Sydenstricker, and the British under Drummond. There were three survey teams provided by the R.C.A.F., the U.S. Army, and the Oxford Nutrition Survey, whose primary function was rapidly to assess the most serious nutritional deficiencies and so to guide Burger's feeding teams. In addition, valuable observations were made by Dutch clinicians. The scientific study of the Dutch famine was handicapped partly by the primary duty of feeding rather than investigating starving persons, and partly by the necessity of making large-scale observations to assess the incidence and type of malnutrition: the Oxford Nutrition Survey team carried out some 25,000 biochemical estimations in five weeks.[5] A preliminary account of all the observations in Western Holland has been published in two volumes under the editorship of Burger, Drummond, and Sandstead.[5]

Certain of those concerned with the study of the Dutch famine went on to Germany in the summer of 1945. Nutritional surveys were organized in the U.S. Zone by the U.S. Army and in the British Zone by the Oxford Nutrition Survey; in addition, a Combined Nutrition Committee consisting of nutritional experts and administrative officials from the three Western Zones visited these periodically and issued authoritative reports on the nutritional situation. One of these reports was published.[6]

Although a few isolated reports of the work of the teams have appeared, the full account of the nutritional situation in Germany and Austria after the war has yet to be written. That it should be written is important not so much for scientific advances that it might contain as for providing scientific evidence of the food consumed by different sections of the population and the effect of this on health. These two types of study cannot easily be combined: the epidemiology of malnutrition is studied by survey teams examining large samples of the population, whereas the science of human nutrition is best advanced by the

1 *Spec. Rep. Ser. med. Res. Coun. Lond.*, No. 77, 1923. London: H.M.S.O.
2 Grande, F., and Peraita, M. *Avitaminosis y Sistema Nervioso*, 1941, Madrid (Editorial Miguel Servet).
3 Apfelbaum, B. (Editor). *Maladie de Famine, Recherches Cliniques sur la Famine exécutées dans le Ghetto de Varsovie en 1942*. 1946. Warsaw: American Joint Distribution Committee.
4 Bigwood, E. J. (Editor). *Enseignements de la Guerre 1934-1945 dans le Domaine de la Nutrition*. 1947. Liége: Editions Desoer.
5 *Malnutrition and Starvation in Western Netherlands, September, 1944–July, 1945*, Parts I and II. 1948. The Hague: General State Printing Office.
6 *Second Review of the World Food Shortage, July 1946*, Appendix A. 1946. London: H.M.S.O. Cmd. 6879.
7 Keys, A., Brozek, J., Henschel, A., Mickelson, O., Taylor, H. L., Simonson, E., Skinner, A. S., and Wells, S. M. *The Biology of Human Starvation*, Vols. 1 and 2, 1950. Minneapolis: University of Minnesota Press.
8 Members of the Department of Experimental Medicine, Cambridge, and Associated Workers. *Studies of Undernutrition, Wuppertal 1946-9*. 1951. Medical Research Council Special Report Series No. 275. London: H.M.S.O.

experimental method of studying nutritional deficiencies induced in man under controlled conditions, or by the detailed observation of a few selected cases of malnutrition spontaneously arising. The first type of study was brilliantly conducted by Keys and his colleagues, and the results were recently published as a classical monograph of 1,385 pages, of which 86 are of references[7]: a number of volunteers were studied in great detail while they subsisted on a diet of about 1,570 calories daily and also during a period of rehabilitation. The second type of study was made under the auspices of the Medical Research Council, and has just been published.[8]

Professor McCance and his nineteen co-authors describe in 20 papers the results of observations made in Wuppertal from June, 1946, onwards. Although, according to their report, "1945 was probably the year in which there was the greatest shortage of food," there were plenty of cases of undernutrition to study in Wuppertal and in a neighbouring prison in 1946. Observations were made on fluid balance, the skin, the alimentary tract, the liver, the parotids, the neuromuscular system, emotional and behaviour reactions, various physical and chemical properties of the blood, the circulatory system, the bones, the size of newborn babies, and the volume and composition of human milk. But apparently the undernutrition, though "serious," was very considerably less than that encountered in Holland: "There were, in fact, none of the signs of really severe undernutrition, and no deaths that could be attributed simply and solely to this cause occurred either in Wuppertal or in the whole of the British Zone"—perhaps a rather rash generalization from studies almost confined to Wuppertal and made after the war, in which there was probably the greatest shortage of food.

To the absence of severe undernutrition is presumably due the essentially negative nature of the report. For instance, although in August, 1946, "the men in Wuppertal had been living for a year on about 35 g. protein, mostly of vegetable origin, per day," hepatic structure and function appeared normal. The cause of the increased extracellular fluid in famine oedema was not elucidated, although some interesting observations were made. Though six out of seven undernourished men were in negative calcium balance, no cases of osteoporosis or osteomalacia were discovered; it is suggested that conditions in Germany had not been bad for long enough for osteoporosis to have appeared. Perhaps the most interesting observations are on the falling serum cholinesterases in undernutrition, and on the size of the baby at birth: as was found in Holland, undernutrition decreases the birth weight. The report contains excellent references to much of the older literature but surprisingly ignores some of the more recent work: of the books cited above, those edited by Apfelbaum,[3] by Bigwood,[4] and by Burger and his colleagues[5] are not mentioned; it is particularly surprising that there is no mention of the report on the Dutch famine, which, though dated 1948, became available in this country in 1949 and is discussed in Keys's great work.[7]

The post-war studies of undernutrition emphasize our ignorance of the causes of many of the phenomena that constitute this condition. But almost all of them are problems that can and should be studied experimentally without awaiting the occurrence of famines.

CORTISONE AND ALLERGY

When once the dramatic effect of cortisone upon rheumatoid arthritis and rheumatic fever had been appreciated, it became only a matter of availability and of time before the effects of cortisone and A.C.T.H. were tried upon many other conditions whose aetiology was frankly allergic or in which allergy was suspected of playing a part. A special issue of the *Bulletin of the Johns Hopkins Hospital* (87, No. 5, 1950) devoted to this subject, as well as many other scattered reports, describes in chronic allergic conditions clinical results which are almost as dramatic as those obtained in rheumatoid arthritis. One paper in the *Bulletin* describes the effect upon drug hypersensitivity reactions of many types, including giant urticaria, angioneurotic oedema, exfoliative dermatitis, and bullous erythema, which were associated with drugs ranging from penicillin to atropine. Others describe the effects of A.C.T.H. and cortisone on chronic bronchial asthma, upon disseminated lupus erythematosus and periarteritis nodosa, and upon certain diseases of the eye similar to those recently commented upon in this *Journal* (June 9, p. 1313). The results were nearly always favourable and sometimes appeared to be life saving. Two interesting points emerge. The first is that in conditions which were not ordinarily self-limiting withdrawal of A.C.T.H. or cortisone was associated sooner or later in more than half with return of symptoms (though often in milder form). The second is that antihistamine drugs had been quite ineffective in any of these patients.

It would clearly be of the greatest interest to know in what way cortisone and A.C.T.H. produce their effects in allergic states. Laboratory observations are complicated by the use of widely differing doses in a variety of animals. The following effects of cortisone appear, however, to be fairly well established.

First, on the negative side, preformed circulating antibodies are not notably affected by cortisone, though prolonged administration of large doses can cause a marked diminution of new formation of antibody. The therapeutic effects of cortisone occur within a few hours of administration, and must therefore initially be independent of changes in circulating antibody. Clearly, however, any allergic reactions dependent upon new antibody formation will be suppressed so long as sufficient cortisone is administered. This last effect resembles that of whole body irradiation with *x* rays.

Secondly, cortisone diminishes only slightly, if at all, the response to locally injected histamine, or to a histamine liberator such as curare. It gives only slight protection against acute anaphylaxis in the guinea-pig, although rather better protection against anaphylaxis in adrenalectomized mice. In agreement with these findings cortisone appears to confer no protection on passive skin-sensitivity reactions of the Prausnitz-Küstner type.[1] These are all reactions which can be virtually prevented by antihistamine drugs. On the positive side, however, slowly developing and more long-drawn-out reactions of the tuberculin-hypersensitivity type in guinea-pigs[2] or man[3] are greatly diminished by cortisone, even in single doses. The same seems to be true of the Arthus reaction (the oedema and necrosis produced by local subcutaneous injection of antigen into sensitized animals), though it is difficult in published papers to disentangle the effects upon the reaction itself and upon the level of circulating antibody upon which the reaction depends. Rich and his colleagues,[4] continuing their studies upon experimental cardiovascular lesions produced by intravenous horse serum injection in rabbits, have found that the incidence of periarteritis and endocarditis was greatly diminished when cortisone was administered throughout their experiments, even though antibody levels were apparently little affected.

Since non-specific chronic inflammation such as Selye's formalin arthritis[5] is also much lessened by cortisone, it is possible that the effect in allergic reactions is no more specific than is the inflammatory response to injury itself. If so, two aspects need to be considered—namely, the erythema and oedema which are obvious to the naked eye, and the cellular changes observed histologically. The erythema and oedema are certainly diminished. There appears, however, to be no clear evidence that the acute polymorphonuclear and macrophage reaction to inflammation is altered, although subsequent development of granulation tissue is markedly suppressed. Cortisone indeed does not greatly affect circulating polymorphonuclear leucocytes other than eosinophils, though the level of lymphoid cells is consistently lowered.

It seems that administration of cortisone prevents increased capillary permeability in these allergic reactions, but no explanation of how it does so is forthcoming. This is perhaps not surprising, since the mechanism of delayed allergic reactions is a mystery, and if histamine plays any part it must be released in a way different from its release in acute anaphylaxis. A direct attempt at studying changes in the permeability of synovial membrane has been made by Seifter and his colleagues,[6] by injecting dye into a joint of a rabbit and measuring the time taken for the dye to appear in the urine. He claims to have observed a marked and prolonged decrease in permeability when 1 mg. cortisone per kg. was administered. The experiment is suggestive, though the technique must be difficult to control. Other rather indirect experiments suggest that treatment with cortisone brings about considerable changes in the state of the ground substance of connective tissue. How far these are bound up with the results of Long and his colleagues, described in an annotation in our issue of July 7 (p. 37), in which a close connexion is shown between cortisone and ascorbic acid in their effects on desensitization in the guinea-pig, it is yet too early to say. In this field, as in others, cortisone is stirring up some fundamental issues.

[1] Stollerman, G. H., Rubin, S. J., and Poltz, C. M., *Proc. Soc. exp. Biol., N.Y.*, 1951, **76**, 261.
[2] Long, D. A., and Miles, A. A., *Lancet*, 1950, **1**, 492.
[3] Long, J. B., and Favour, C. B., *Bull. Johns Hopk. Hosp.*, 1950, **87**, 186.
[4] Rich, A. R., Berthrong, M., and Bennett, I. L., Jun., *ibid.*, 1950, **87**, 549.
[5] Selye, H., *British Medical Journal*, 1949, **2**, 1129.
[6] Seifter, J., Baeder, D., and Begany, A. J., *Proc. Soc. exp. Biol., N.Y.*, 1949, **72**, 277.

INTRAVASCULAR THROMBOSIS

There has been much speculation about the causes of thrombosis. To some it has seemed obvious that there must be an increased coagulability of the blood before clotting can occur in the vessels. Others have thought that stasis of normal blood is sufficient to induce clotting. Although many tests have been carried out on the blood of patients after operation and on the blood of those with coronary thrombosis, no reliable evidence of increased coagulability has ever been found, and it is doubtful if any such change will be demonstrated. Normal blood withdrawn from the body clots with great rapidity, and it is more surprising that the blood fails to clot in normal vessels than that it occasionally clots in patients with disease.

The work of Raeburn, reported elsewhere in this issue, supports this view. Raeburn made a careful study of the veins of the leg in 130 unselected necropsies. He found that thrombosis could be demonstrated in 35

patients (26.9%). Of these, 19 showed evidence of recurrent thromboses, and in 20 pulmonary emboli were present. The amazing frequency with which thromboses were found when carefully sought suggests that thrombosis is prevented in normal people by the constant activity of normal life, and that the stasis induced by restriction to bed is sufficient to induce thrombosis in very many cases. It is true that some of the thromboses Raeburn found may have been terminal, but on the other hand there were also residual thrombotic lesions which indicated that thrombosis had occurred some considerable time before death. Many of Raeburn's necropsies were carried out on elderly patients or those who had been restricted to bed for long periods of time before death. His findings emphasize the danger of prolonged treatment in bed, particularly in the elderly.

These observations are especially important for the treatment of coronary thrombosis with anticoagulant drugs. Since there is now no doubt that anticoagulant therapy prolongs the life of these patients the drugs are widely used. The duration of treatment is variable. Some think that three weeks will tide the patient over the most dangerous period, others that the treatment should be continued while the patient is in bed. If, as Raeburn's results suggest, restriction to bed is sufficient to induce thrombosis in those with no serious cardiovascular disease, it is obvious that prolonged rest is particularly dangerous to patients who have developed thrombosis while carrying out their normal activities. Anticoagulant therapy should logically be continued as long as the patient is in bed, and there is some justification for the view that it should be extended indefinitely in those whose normal activity is necessarily much reduced.

CLINICAL USE OF HYALURONIDASE

In 1928 Duran-Reynals[1] described how a testicular extract added to vaccinia virus injected intradermally made it spread through a greater area. Subsequently a similar effect was found to be produced by the addition of a variety of extracts—from semen, snake venom, and skin, and from various bacterial cultures, both aerobic and anaerobic. In this country McClean[2] published the results of his work on this spreading phenomenon in 1930. In 1939 Chain and Duthie[3] showed that the effect of the extracts was due to an enzyme capable of hydrolysing hyaluronic acid. They called this enzyme hyaluronidase.

Hyaluronic acid is a polysaccharide present in mucoprotein, a constituent of the viscid ground substance of the intercellular connective tissue of the body. When it is depolymerized by hyaluronidase, resistance to the passage of fluid is much diminished. It was this finding that suggested the clinical use of the enzyme as an adjuvant to hypodermoclysis. Hechter[4] in 1947 showed that there must be an increase in the cellular interstitial pressure before hyaluronidase can exert its effect. Such increase occurs naturally in inflammation, from the accompanying oedema, but in hypodermoclysis the injected fluid provides the requisite added pressure.

Hyaluronidase has been found in certain bacterial infections, in which it is known to play an active part, since the increase in tissue permeability resulting from its liberation may be responsible for the spread of infection. It has been suggested also that it is concerned in the pathology of rheumatic fever, and this aspect is now the subject of investigation. The enzyme's action is inhibited by antihistaminics and by sodium salicylate, and its local effect is diminished by heat.

One of the practical difficulties encountered in the therapeutic use of an enzyme is the provision of a satisfactory method of assay, without which dosage cannot be accurately gauged. Several methods have been suggested for standardizing hyaluronidase: viscometric, turbidometric, and neutralization by specific antihyaluronidase. It is likely that a standard method will be agreed upon in the near future.

Although its value in therapeutics can be regarded only as ancillary, hyaluronidase nevertheless has proved its worth. After a series of animal experiments in which the enzyme was found to be completely non-toxic, it was used clinically by Schwartzman and his colleagues[5] in 1948 to assist the absorption of glucose-saline given subcutaneously to dehydrated infants. The increased tension resulting from injected fluid is lessened by hyaluronidase so that large quantities may be injected rapidly without pain; intramuscular injections and subcutaneous infusions can be used freely and repeatedly. Thus 150–250 ml. of glucose-saline or plasma may be injected subcutaneously into an infant in a few minutes and absorbed in a few hours through the increased absorptive area with which the fluid is brought into contact.

Its use has subsequently been extended to include the injection of local anaesthetics, parenteral drug administration, and alimentation (plasma and glucose or amino-acid solutions which are commonly given intravenously may be absorbed from the subcutaneous tissue), and subcutaneous pyelography. As an example, a practitioner faced with a Colles fracture to reduce without a general anaesthetic may with the use of hyaluronidase inject a sufficient quantity of local anaesthetic to enable the reduction to be effected painlessly. In obstetrics the addition of hyaluronidase to the analgesic agent has been found valuable in pudendal block.

The technique of injection has been fully described and presents no difficulties.[6] The enzyme is provided as a freeze-dried powder which is instantaneously soluble in water. The syringe and needle used must be free from contamination with any antiseptic which would inactivate the enzyme, and the powder should be freshly dissolved in cold water immediately before use. In the dried state it keeps indefinitely at ordinary temperatures without any deterioration, but is soon inactivated in solution.

One of the peculiarities—and a distinct advantage—of hyaluronidase is that it may be used even when there is skin sepsis present, without causing a spread of infection. Hechter has shown that hyaluronidase takes the

1 *C.R. Soc. Biol., Paris*, 1928, **99**, 6.
2 *J. Path. Bact.*, 1930, **33**, 1045.
3 *Nature, Lond.*, 1939, **144**, 977.
4 *J. exp. Med.*, 1947, **85**, 77.
5 *J. Pediat.*, 1948, **33**, 267.
6 Evans, D. G., Perkins, F. T., and Gaisford, W., *Lancet*, 1951, **1**, 1253.

line of least resistance and will diffuse around any infected area, but not through it, the fibrin surrounding the area forming an effective barrier.

Used in the proper manner, and with due regard to its limitations, hyaluronidase will prove a valuable addition to the practitioner's equipment.

TUBERCULOSIS IN ADJACENT HOUSES

The spread of tuberculosis is a slow process compared with other infectious diseases, and the length of the interval between infection and the development of clinical symptoms makes it very difficult and often impossible to trace the source of infection. It is well established that tuberculosis is liable to spread to all the members of a household once it is introduced, and Webb, Stewart, and Sutherland[1] have now attempted to trace the spread of tuberculosis from house to house. Their data consisted of the records of the tuberculosis notifications in Northampton between the years 1921 and 1948. This town compares very favourably with other county boroughs in general sociological features, and the tuberculosis death rate has been similar in age and sex distribution and in trend to the rate for the whole country. Notifications of one form of tuberculosis had been received from 2,871 houses, one-tenth of all the houses of the town, during the period under review, and of the 640 streets 82 were free of tuberculosis during this time. The next-door pairs of houses and houses separated by one to five unaffected houses were counted. The authors found evidence that there was a slight tendency for tuberculosis to pass from one house to its neighbour during 12 years from the notification of the original case—i.e., tuberculosis tended to occur more often and in a shorter space of time in next-door houses than would be expected if the cases had been randomly distributed throughout the town. The transmission of infection to immediate neighbours was less in the "good" type of house than in the "fair" or "poor" type. The grading of houses by the social status of the householder showed that for social classes I and II the spread of infection was less than for the other classes. An examination of the relationship of persons living next door to one another showed that the spread of infection was not due to a large proportion of neighbours being related, and presumably it is direct contact which was responsible.

It is possible that in some cases neighbouring households were infected independently from a common source. The boot-and-shoe trade has an excessive tuberculosis risk compared with other occupations in Northampton. Slightly more than one-quarter of all males aged 14 and over are employed in it, and these workers had a notification rate of tuberculosis twice as high as the other male inhabitants aged 14 and over—23.8 per 10,000, compared with 12.4. The female boot-and-shoe operatives also had an attack rate almost twice that of the remaining females. If these workers are not randomly distributed among the houses, but tend to be congregated, then it is possible that an occupational risk is superimposed on the neighbourhood risk. The authors have not examined this point, which might be sufficient to upset their conclusions.

1 *Brit. J. soc. Med.*, 1951, **5**, 13.

PARTITION CHROMATOGRAPHY

"Like the light radiations in the spectrum, so is a mixture of pigments systematically separated on the calcium carbonate column into its constituents. . . ." In these words Tswett, a botanist from Warsaw, described in 1906 the changes he saw taking place when a mixture of plant pigments dissolved in light petroleum was allowed to percolate slowly through dry calcium carbonate packed tightly into a long glass tube. Tswett realized that the constituents of the mixture were separating from each other as the result of their different affinities for the calcium carbonate. Those with the greatest affinity stuck to the chalk more firmly and remained near the top of the column, while those with less affinity moved slowly down the column at different rates. He had a vision also of the future, for he clearly stated that his new method of separating the components of mixtures should be applicable to many substances other than the plant pigments with which he had first demonstrated its use. But his pioneering effort was not fully exploited until after 1930, and it was not till 1941 that a completely new modification was introduced. This was the "partition" chromatogram of Martin and Synge.[1] The novelty here was that the glass tube was filled not with a dry adsorbent powder but with a hygroscopic substance, such as silica gel, which in itself had no affinity for the constituents of the mixture to be separated. The silica gel was deliberately wetted before being packed into the glass tube, and was then used in the same way as the Tswett columns. But the separations now occurring were the result not of the different adsorptive powers for the substances in the mixture—these are always capricious in the best of circumstances—but of their different "partition" coefficients, that is, the quantitative manner in which they distribute themselves between the stationary water held on the silica gel and the solvent moving down the column. This novel feature enabled the scope of the chromatographic method to be very greatly extended, especially to lower molecular weight compounds such as amino-acids. Since the behaviour of such compounds on the chromatograms was now fairly consistent and followed known physical laws, the method could be used to identify unknown naturally occurring substances.

A very neat application of the technique is in the form known as paper chromatography. This was introduced in 1944 by Consden, Gordon, and Martin[2] for the separation and identification of the amino-acids present in protein hydrolysates. Pieces of filter paper are used

1 *Biochem. J.*, 1941, **35**, 1358.
2 Ibid., 1944, **38**, 224.
3 Dent, C. E., *Lancet*, 1946, **2**, 637.
4 ——, *Biochem. J.*, 1947, **41**, 240.
5 —— and Walshe, J. M., *Conference on Liver Disease*. Ciba Foundation, July, 1950, In press.
6 Biochem. Soc. Symposia, No. 3. *Partition Chromatography*. October, 1948. 1950.
7 Horrocks, R. H., and Manning, G. B., *Lancet*, 1949, **1**, 1042.
8 *Ann. Rev. Biochem.*, 1950, **19**, 517.

as the chromatographic matrix, the cellulose fibres of which it is composed being sufficiently hygroscopic to hold on to a thin film of water. The moving solvent used for affecting the separations is then allowed to soak along it by capillary attraction. The paper may be used in the form of strips, which are hung over the side of a trough containing the solvent; the mixture to be separated is first applied to a small area near the upper end of the paper, so that the solvent slowly soaks past it.

A better method, however, employs squares of filter paper, the mixture being applied near one corner and two solvents with very different properties being used one after the other in directions at right angles. The substances in the mixture first move down the paper at rates characteristic for the first solvent, and then across the paper at other speeds characteristic for the second solvent. In this way the amino-acids are well separated spatially, and each comes to occupy a small area of the paper, where it is finally detected by the purple colour reaction given after the paper has been sprayed with a solution of ninhydrin and warmed. This two-way procedure greatly increases the efficiency of the separations and is essential in identifying very complex mixtures.

An early trial soon showed that this beautiful technique could be applied to the investigation of medical problems, minute quantities of amino-acids in a single drop of human urine being detected readily enough on paper chromatograms.[3] The result of each analysis was a large sheet of filter paper covered with up to 20 purple spots: the identity of the amino-acids was accurately indicated by the positions of the spots, while the strength of the colour reaction showed roughly the amount of each amino-acid present. Further, it was soon shown that not only the amino-acids but also all the other common constituents of urine—urea, glucose, creatinine, and inorganic salts—also migrated characteristically and could be found occupying appointed places on the paper.[4] The spate of articles published subsequently on various developments of the method show that paper chromatography is no less than a new general method of chemistry and is capable, when applied to biological fluids, of revealing a new world of hitherto unknown facts. It now completely outdates the older methods for identifying, say, cystine or reducing sugars in urine. So far its main clinical application has been in the study and diagnosis of disorders of amino-acid metabolism; acute and chronic liver disease[5]; and certain congenital conditions such as phenylketonuria, the Fanconi syndrome, hepatolenticular degeneration, and cystinuria.[6] But the scope of the method is being rapidly extended to include many other substances, such as purines, porphyrins, sugars, organic acids, steroids, vitamins, and inorganic ions. Unfortunately no concise up-to-date account has yet been published of the detailed techniques which are of immediate value for medical diagnosis and research. A review of the literature to the end of 1948 is available, together with some accounts of particular applications.[6] An article on the identification of sugars in urine also exists,[7] and Martin[8] has recently reviewed the application of the method to other substances.

TREATMENT OF MIGRAINE

There is at present fairly general agreement that the mechanism of production of symptoms in an attack of migraine is essentially vascular. The aura, which may consist of sensory symptoms or dysphasia as an alternative to the more common visual phenomena, is probably caused by constriction of cerebral arteries, while the headache results from dilatation and distension of cranial arteries, particularly in the distribution of the external carotid. The basic cause of migraine, however, is a more complex problem; in particular, the nature of the stimulus which sets the vascular disturbance in motion is not clear. The constitutional factor is probably the most important, but allergic, endocrine, refractive, and psychological abnormalities, among others, have been thought to play a part. Treatment is often most unsatisfactory, as many sufferers from the disorder will agree. Friedman and von Storch[1] have compared the results of various methods in a series of 600 patients whom they had under observation for from one to four years and in whom fairly strict criteria for the diagnosis of migraine were used. They concentrated their attention chiefly on the treatment of the actual attack, and agree with others that ergotamine tartrate is the most useful drug. Oral administration gave good results in only 45% of cases, but injections of this drug or of dihydroergotamine were of value in 80%. They obtained even better results with a preparation containing 1 milligram of ergotamine tartrate and 100 milligrams of caffeine. When given by mouth this eased the headache in as many as 86% of the patients. It is well known that some patients, though relieved of migrainous headaches by ergotamine, suffer so much from nausea when taking the drug that they actually prefer migraine: the authors do not state whether they regard such patients as "improved." Their results with ergotamine either by injection or by mouth are better than those often seen in migrainous patients, but it certainly seems that the combination of ergot and caffeine given orally should be given a thorough trial. Friedman and von Storch found other vasoconstricting drugs of value only in occasional patients, and simple analgesics and vasodilators were not often helpful.

In an attempt to lessen the frequency of attacks of migraine these authors relied mainly on psychotherapy: this took the form of analytically orientated interviews with psychiatrists, though formal psycho-analysis was not attempted. The frequency of attacks was reduced in 66% of the patients treated in this way over a period of two to four years. Other methods of prevention, such as intravenous histamine infusions, antihistamine drugs, nicotinic acid, thiamine chloride, and testosterone were relatively unsuccessful. In the discussion on this communication most speakers agreed on the value of ergotamine in aborting individual attacks. But it must be remembered that the repeated administration of large doses may be dangerous. Peters and Horton[2] have recently recorded toxic effects—ischaemic neuritis in one leg, vasospasm in digital arteries, precipitation of anginal pain, and abdominal pain and anuria—in six patients.

[1] *J. Amer. med. Ass.*, 1951, **145**, 1325.
[2] *Proc. Mayo Clin.*, 1951, **26**, 153.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

SPECIFIC TREATMENT OF INFECTIONS OF THE EYE

BY

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Present-day treatment of infections of the eye is highly specific and thus calls for specific diagnosis. Such general terms as conjunctivitis and keratitis are an inadequate basis for effective treatment, for they imply little more than that there is a lesion of the conjunctiva or cornea. The sulphonamides and the antibiotics being specific agents for the treatment of infections due to susceptible organisms, the first step is to establish clinically in all cases, and bacteriologically where possible, that the lesion in question is indeed an *infective* lesion and not merely an inflammatory reaction. Such inflammatory reactions as phlyctenular ophthalmia, and the mass of nondescript lesions labelled chronic conjunctivitis, are not infective in character and their treatment by sulphonamides or antibiotics is a futile abuse of valuable agents. A clear understanding of the infective lesions of the eye as distinct from the inflammatory reactions is therefore essential if any results are to be obtained at all. For the best results it is equally essential to possess a working knowledge of the different types of infection. The infections of the inner eye are grave emergencies that must be left to the expert ophthalmologist.

The sulphonamides, penicillin, and streptomycin used locally are not free from irritative reactions; but, as the sulphonamides, though widely used, are of exceedingly limited value in ocular infections except trachoma, the irritative reactions are of no great importance. Such irritative reactions as occur with penicillin are almost entirely due to the use of impure brands. When white crystalline penicillin is used reactions are exceptional with drops, and almost equally exceptional with ointments if a suitable ointment base is employed; the more complex ointment bases are best avoided, and a simple base such as 90% petroleum jelly and 10% liquid paraffin gives excellent results. Reactions are still less likely if the penicillin is incorporated in powder form into the base and not first dissolved.

Streptomycin, even in purified preparations, is rather more apt to give irritation, but this is not likely to occur except with prolonged use. As both penicillin and streptomycin are quickly effective if they are used adequately and in suitable cases, the question of irritative phenomena is largely an aspect of the abuse of these agents rather than a complication of their rational use.

Infections of the Outer Eye

The infections of the outer eye include such severe affections as purulent conjunctivitis, with its immediate threat to sight from corneal complication, and relatively mild affections such as chronic blepharitis. It is no academic exercise to recognize clearly the clinical features of these different infections, as treatment is determined by this knowledge.

Purulent and Mucopurulent Conjunctivitis.—A red eye is not evidence of infection. The eye may be congested from an attack of acute or subacute glaucoma, or of acute iritis. Definite evidence of infection is presented by a purulent or mucopurulent discharge from the conjunctiva. In the absence of such discharge the presumption is in favour of an inflammatory reaction rather than infection, except that infection with non-pyogenic viruses produces a conjunctival reaction largely indistinguishable from inflammation. Purulent conjunctivitis, typically seen in ophthalmia neonatorum, may be caused by many different organisms. An accurate bacteriological examination is generally of no great importance, as most pyogenic organisms are sensitive to both penicillin and the sulphonamides. Exceptionally pyogenic reactions are due to Gram-negative bacilli, which do not respond readily to either sulphonamides or penicillin, but respond well to streptomycin. If within 24 hours of instituting adequate penicillin or sulphonamide therapy the infection is not well under control, one may safely assume that it is due either to Gram-negative bacilli or, more rarely, to insensitive strains of organisms which are normally sensitive to the sulphonamides and penicillin.

Infections of the Cornea.—Differential diagnosis in corneal lesions is particularly difficult. Many corneal lesions are inflammatory rather than infective. Some of the inflammatory reactions may be due to infection by non-pyogenic viruses; some, such as phlyctenular ophthalmia and interstitial keratitis, are allergic or anaphylactic in type; some, like the corneal dystrophies with their distinct mode of inheritance, are genetically determined. Of the frank infections of the cornea, by far the commonest is the group of serpiginous ulcer with greyish, obviously infected margins and hypopyon. Here the pneumococcus is a frequent, though by no means the commonest, infecting organism, staphylococci and streptococci being responsible for most cases. These are penicillin-sensitive organisms, and response to modern treatment is excellent—a striking contrast to the poor results obtained in the past. Occasionally an infected corneal ulcer is caused by Gram-negative bacilli. The clinical picture is generally characteristic. Instead of an infected serpiginous margin, there is a sloughy heaped up base, with a good deal of diffuse corneal infiltration—the effect of the proteolytic action of these organisms. Hypopyon is not a striking feature in this type of reaction. These cases do particularly badly if inadequately treated, and do not respond to penicillin.

Acute Virus Infections of the Conjunctiva and Cornea.—The virus infections of the conjunctiva and cornea are exemplified by epidemic kerato-conjunctivitis and superficial punctate keratitis. Here there is neither purulent nor mucopurulent reaction, but a watery discharge with considerable discomfort; frequently there is a history of an acute respiratory affection. These cases are not readily distinguished from inflammatory reactions, except in the acute stage

"Chronic Conjunctivitis."—Chronic inflammatory reactions of the conjunctiva—the conditions passing under the name of "chronic conjunctivitis"—are a difficult aetiological group. Persistent treatment with

the sulphonamides and penicillin only aggravates matters, for drug irritation is added to the inflammatory reaction.

Blepharitis.—Inflamed lid margins, especially when acute, may be due to rubbing of the eyelids or to infection spreading from the conjunctiva. The primary lesion should be established and treated. Most cases are, however, of the primary chronic type.

Ophthalmia Neonatorum

Only some 20% of cases of ophthalmia neonatorum are caused by the gonococcus. A considerably greater proportion are caused by the staphylococcus, and most of the common pyogenic organisms contribute a quota. Some 10 to 20% of cases are caused by a pyogenic virus, morphologically similar to the virus of trachoma. Fortunately all these organisms are sensitive to the sulphonamides and to penicillin, though to a variable degree. Maximum dosage of the agent employed is therefore essential if the relatively insensitive organisms are to be caught as well as the more sensitive ones.

There are two alternative methods of treating ophthalmia neonatorum. The easier, though somewhat slower, method is the oral administration of sulphonamides. Treatment with penicillin locally gives incredibly rapid results, but calls for considerably more nursing care. As a routine method, where no special facilities are available, treatment by oral sulphonamides is the method of choice. Whichever method is used, meticulous attention to detail is essential.

Before beginning treatment a swab should be taken for smear and culture, and the eye irrigated with half-normal saline at room temperature. Where facilities are available a drop of adrenaline 1 in 1,000 should be instilled and a scraping taken from the palpebral conjunctiva for examination for the presence of inclusion bodies. In all cases atropine sulphate drops, 1%, are instilled if the cornea is hazy. Any pus that may have accumulated is wiped away with moist pledgets of cotton-wool.

Oral Sulphonamide.—After the above preliminary measures a tablet of sulphamerazine (0.5 g.) crushed into powder is given by mouth in a teaspoonful of water or milk. Sulphamerazine administration in doses of 0.25 g. is continued every 8 hours, until 48 hours after clinical cure. (If sulphadimidine is used the administration has to be at six-hourly intervals.) Local treatment consists in three-hourly irrigation with isotonic saline solution during the first day in cases with profuse discharge; as a rule there is no need for further irrigation on the subsequent days. After irrigation medicinal paraffin is instilled as a precaution against the sticking together of the lids. With this treatment swelling of the lids generally subsides within 12 hours, and the purulent discharge disappears within 24 hours.

Local Penicillin.—After the same preliminary measures as with oral sulphonamide therapy, a drop of penicillin in a concentration of 10,000 units per ml. is instilled into the conjunctival sac. The baby is now placed on the nurse's lap, while another nurse sitting near instils one drop of penicillin solution, 10,000 units per ml., every minute for 30 minutes. Irrigation is not needed, as pus does not form to any extent; such thin mucoid discharge as is present can be ignored or, if it clings to the lid margin, wiped away with moist pledgets of cotton-wool. At the end of this time there is invariably no pus and generally little or no discharge. The eye, however, is still moist, the lids are still swollen, and the lid margins tend to be sticky. The baby is returned to its cot, and penicillin drops are instilled six times at five-minute intervals, followed by a similar number of instillations at half-hourly, hourly, and two-hourly intervals. This gives a total of 22 hours' treatment. Many cases require no further attention. In some babies the lid margins still tend to remain sticky, and it is advisable in such cases to continue with penicillin at two-hourly intervals until the eye is dry, when treatment is carried on for a further 12 hours. Crystalline penicillin only should be used for making up the drops, as impure penicillin is likely to cause irritative reactions.

Exceptionally the response to one or other method is not as good as might be expected. In such cases it is essential to change over from one method to the other, and to be guided by bacteriological tests. Rarely streptomycin may have to be used. In no case should local sulphonamides be employed. They are ineffective in checking a purulent infection, and as such their use is dangerous.

Purulent Conjunctivitis in Adults

This, too, may be caused by a variety of different organisms. There is no fundamental difference in treatment from that employed for ophthalmia neonatorum except that if oral sulphonamide is used full adult doses should, of course, be given.

Mucopurulent Conjunctivitis

These cases generally respond rapidly to modern treatment. It is unnecessary to use sulphonamides systemically, for local penicillin therapy is simple and adequate. Any excessive mucopurulent discharge can be washed out from the conjunctival sac with lukewarm water. Penicillin ointment, containing 1,000 units of crystalline penicillin per gramme, can then be instilled two-hourly during the day. Within 24 to 48 hours the eye should be normal. The local use of sulphonamides, though widely practised, is quite valueless.

Acute Virus Conjunctivitis

Epidemic kerato-conjunctivitis is endemic rather than epidemic in this country. There is conjunctival injection, watery discharge, some photophobia, and often an enlarged pre-parotid node, unilateral if only one eye is affected. A history of an acute respiratory infection is common. If corneal involvement supervenes this takes the form of superficial punctate keratitis, demonstrable on staining with fluorescein and by the increase in symptoms. There is no response to the sulphonamides, penicillin, or "aureomycin." Non-specific measures, such as the use of silver nitrate, produce only further irritation. There is at the present no specific treatment, though there is some hope in one of the newer antibiotics.

Trachoma

Trachoma is still the largest single blinding disease in the world. In this country it has been a mass problem only on occasions, and never in recent times; to-day fresh cases are seen only exceptionally. In Ireland it still appears to be a serious issue.

Mechanical expression of follicles is still an important part of present-day treatment of trachoma, but most agents used in the past are now obsolete. After expression the fornix should be painted with 30% sodium sulphacetamide daily for a month or so. Sulphacetamide ointment, 6% in a base consisting of 90% petroleum jelly and 10% liquid paraffin, should be used three

or four times daily. Fresh cases without marked corneal involvement recover rapidly. When the cornea is involved atropine sulphate drops 1% may have to be used three times daily to keep the pupil dilated. If a patient suffers from secondary infection of the conjunctiva when first seen, full doses of oral sulphonamides for three to four days should be given before undertaking expression of follicles and local therapy.

The value of aureomycin and chloramphenicol in trachoma still remains to be assessed.

Infections of the Cornea

Unless a diagnosis of infection by Gram-negative organism is made on clinical grounds when the patient is first seen, every case should be treated at once on the assumption that it is caused by a penicillin-sensitive organism, but a swab from the conjunctival sac should always be taken for bacteriological examination. If, after 24 hours, penicillin treatment has not produced a marked improvement, and particularly so when the culture shows no organisms or reveals Gram-negative organisms, the penicillin should be discontinued.

Serpiginous Hypopyon Ulcer or Other Corneal Infection Due to Penicillin-sensitive Organisms

It is possible that full doses of sulphonamides orally will give good results, but the best results are obtained by subconjunctival injection of penicillin. The procedure is as follows: Any sticky discharge present is washed away by cotton-wool swabs moistened in lukewarm water. Two drops of 4% cocaine are instilled into the conjunctival sac three times, at intervals of two to three minutes, the eye being kept closed during that time. With the eye adequately cocainized the subconjunctival injection can be easily given. This contains 1,000,000 units of crystalline penicillin dissolved in 10 min. (0.6 ml.) of sterile water and 5 min. (0.3 ml.) of adrenaline 1 in 1,000. A simple way to obtain this solution is to inject these quantities direct into a bottle containing the crystalline penicillin and shake the solution. The clear solution can then be withdrawn into a syringe fitted with a small needle, such as a tuberculin needle, and the injection made subconjunctivally at about 4 or 5 mm. from the limbus. It helps matters if someone else can keep the lids separated while the injection is made.

The use of adrenaline ensures that the penicillin does not diffuse too readily into the surrounding tissues, and in consequence the intraocular level reached is high and also more persistent. Patients generally tolerate subconjunctival injections well, and there is usually no difficulty in giving a second or third injection at intervals of 24 hours if necessary. However, any but the most severe hypopyon ulcer will have responded well to one injection, so that if the hypopyon has disappeared, or almost disappeared, within 24 hours a second injection is unnecessary. Continued treatment is, however, a matter of some importance. The intraocular level of penicillin can be maintained at a therapeutic point by instilling penicillin ointment, containing 100,000 units per gramme, at intervals of two hours for a further two to three days.

Proteolytic Corneal Ulcer Due to Gram-negative Bacilli

These cases can be satisfactorily treated by subconjunctival injection of 0.5 g. of streptomycin in a manner similar to penicillin injection. Generally two or three injections at intervals of 24 hours are necessary. As with penicillin therapy, maintenance treatment should be continued when the subconjunctival injections are no longer necessary: streptomycin ointment containing 0.1 g. per gramme should be instilled at two-hourly intervals during the day for two to three days.

Cases Showing No Organism

As all cases will have received penicillin subconjunctivally (or streptomycin exceptionally) the response will guide further treatment. If the patient is doing well on penicillin the negative bacteriological report should be ignored. If the response is poor after 24 hours streptomycin should be used, for the Gram-negative infections are often not readily demonstrated bacteriologically.

Adjuvant Treatment

All cases require atropine sulphate drops 1% instilled three-hourly in the affected eye. Where facilities exist, the solvent used for dissolving the penicillin or streptomycin may carry 1/60 or 1/40 gr. (1 or 1.5 mg.) of atropine sulphate and 1/10 or 1/8 gr. (6.5 or 8 mg.) of cocaine hydrochloride per 10 min. (0.6 ml.).

Treatment of Blepharitis

Chronic simple blepharitis is generally due to a low-grade infection by penicillin-sensitive organisms. The treatment is simple and consists in removing such scales or scabs as are present with cotton-wool swabs moistened either with hydrogen peroxide (10 vols.) or with alkaline solution containing 4 gr. of sodium bicarbonate to the fluid ounce (1 g. to 113 ml.). When the lid margins are quite clean penicillin ointment containing 1,000 units of crystalline penicillin per gramme should be applied (the ointment base being, as already indicated, 90% petroleum jelly and 10% liquid paraffin, and the penicillin being directly incorporated in the base in crystalline form and not in solution). This procedure should be repeated nightly for a fortnight or so. Most cases will have responded well. An alternative and older method is to paint liquor tinctorium *B.P.C.*, instead of penicillin ointment, on to the lid margin. This method may well be used where penicillin treatment has failed. Chronic blepharitis is, however, often an expression of poor nutrition, so that relapses are not uncommon unless general measures are also undertaken.

Dr. J. Heller and his colleagues of the Hôpital Boucicaut in Paris have just published in *La Semaine des Hôpitaux de Paris* of August 26 an electrocardiographic study of 354 cases of angina of effort, together with radiographic measurements of the heart volume and clinical study of the cases with special attention to the possible aetiology. The cases chosen all had attacks of pain strictly provoked by exercise (walking), the attacks lasting at the most 15 minutes (patients with more prolonged pains were omitted from the analysis), and in every case the E.C.G. was taken with precordial recordings V_1 to V_7 as well as the standard and unipolar limb leads. Among their conclusions the authors note that nearly all (99%) of their patients were aged 40 or more, that nearly half of them had a perfectly normal E.C.G., and that coronary thrombosis occurred in 33 cases (9.3%): two-thirds of these infarcts were not preceded by any typical long attack of pain. One of the aetiological factors they investigated was sex, and in particular whether the onset of the menopause influenced the appearance of angina of effort in women. They studied 70 cases with normal menopause, the average age of onset being 48, and 19 younger women in whom it had been artificially induced for various reasons, and were unable to find any correlation between date of menopause and date of first anginal attack.

CASUALTY EVACUATION BY HELICOPTER IN MALAYA

BY

E. BRUCE HARVEY, M.R.C.S., L.R.C.P.

Wing-Commander, R.A.F.

A signal recently received from R.A.F. Headquarters Far East stated : " Helicopters have been doing excellent work and surpassed all expectations. Although sent out mainly for operational trials, have met 90% of calls for casualty evacuation."

FIG. 1.—Westland S.51. (Reproduced by courtesy of *The Aeroplane*.)

The first request for helicopters to evacuate casualties was made by Far East Headquarters in 1949, as Army patrols receiving casualties were unable to continue operations and had to hand-carry their wounded to the nearest road, a journey which often involved several days. At that time the only helicopter in production that had passed its service trials and which was suitable for the task of evacuating casualties was the Westland S.51, or " Dragonfly " (Fig. 1). This type of helicopter normally carries a crew of two and two passengers, has a cruising speed of 70 knots and, with full payload, has a range of 200–250 miles (322–402 km.). It was decided to get three of these aircraft and adapt them for the movement of casualties. As the cabin was not large enough to accommodate a patient on a general service stretcher, it was decided to fit two special containers or " pods " outside the cabin, one on each side of the aircraft. These pods, which were rather coffin-like in appearance, were fitted with windows and controllable air vents. Means of intercommunication with the cabin was also installed.

While these modifications were being carried out the opportunity was taken to visit Malaya and get a first-hand picture of the problems involved.

Nature of the Terrain

Most of Malaya is low-lying, with the exception of some high ground which runs up through the western central side of the peninsula. It is largely covered with primary jungle, where the average height of the trees is 100 ft. (30 m.), and viewed from the air has the appearance of a large cauliflower patch (Fig. 2). There is little undergrowth in this type of jungle, the ground surface is poor, and there is little light; patrols can rarely see the sky. The remainder of the country is covered by secondary jungle or cleared primary jungle which has been allowed to grow again. The undergrowth is very thick and there is a constant struggle for air and light. Rivers and tracks wind among the jungle and are difficult to see until one is directly above them. There are occasional clearings which seem to be good alighting areas when seen from above, but closer inspection reveals waterlogged paddy fields.

The weather is tropical. Frequent early morning mists prevail in the centre of the country; these lift and break into low-layer cloud by mid-morning, becoming strato-cumulus and cumulus by midday, and usually dispersing in the evening. Scattered storms, producing a heavy rainfall, occur during the latter part of the day. Winds are unpredictable at heights at which helicopters operate, usually about 2,000 ft. (610 m.). Violent turbulence is experienced in the bowls at the end of passes through high ground.

While in the Far East it was learnt that calls for helicopter evacuation would occur on an average about once a week, and that, in addition to the task of rescuing Army casualties from jungle clearings, the helicopters would also be useful for taking medical assistance to crashed aircraft and rescuing injured members of the crew. On return to England it was therefore recommended that each helicopter should be fitted with a winch with a form of boatswain's chair attached to the end of the cable.

The aircraft were completed and despatched by sea to Singapore in the spring of 1950. As this type of aircraft had not been operated in tropical climates, the Army authorities were warned not to expect 100% reliability immediately, as the aircraft would have to be tested under the new conditions and the pilots would have to gain experience in flying over and landing in jungle country.

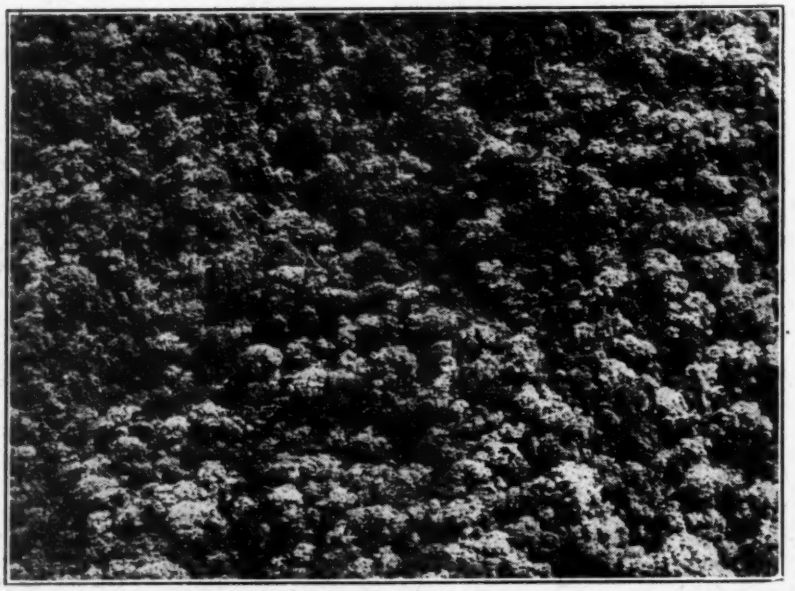


FIG. 2.—Typical Malayan jungle as seen from the air. It is not uncommon for these trees to reach a height of 200 ft. (61 m.). The trees in many cases are festooned with creepers.

Early Difficulties

An R.A.F. casualty air evacuation flight, consisting of experienced helicopter pilots, ground mechanics who received a special course of training in helicopter servicing, and three air-ambulance orderlies, was formed in the United Kingdom and proceeded to Singapore, where active training began. Soon afterwards the first successful evacuation of a casualty was carried out.

One of the earliest lessons learnt was that the "pods" interfered with the performance of the aircraft when operating in the Tropics. These were removed and a wickerwork "cradle," which was made locally, was attached to a metal rack fitted inside the cabin of the aircraft. As a result, owing to the narrow width of the cabin, the foot end of the cradle projected through the door. However, the patient was well protected by coverings and experienced no unpleasant effects. A new method to overcome this has now been devised. This is known as the "top hat" modification, and consists of two bulges in the fuselage to contain the head and foot of the cradle.

On active operations the pilots have found difficulty in navigation and landing procedure, especially in tropical rain. It was therefore decided to replace the air-ambulance orderly by a second pilot who had received a full course of first-aid training. Winching trials have been undertaken, using Neil Robertson's and general service stretchers, but these tend to swing when within 20 ft. (6 m.) of the aircraft. Lowering of a medical officer by means of the winch has been done successfully, and further trials are being carried out.

Landing

It is not easy to find landing grounds prepared by patrols. The usual practice is for an Army Auster plane to reconnoitre the site first and guide the patrol to an appropriate clearing and give it instructions in the preparation of the landing area. The Auster then returns to a strip where the helicopter is waiting, and the pilot is briefed; if necessary the Auster is used to guide the helicopter to the landing area, and constant communication between Auster pilot, helicopter pilot, and ground patrol is maintained by means of radio telephones. Should heavy rain occur the helicopter pilot has to fly around it, or reduce speed to 25 knots and fly low along the line of communication, or land at a strip and wait for the storm to pass, which it usually does in about 30 minutes.

The following are the requirements for a landing ground: (*a*) where possible, level ground should be used; (*b*) an area 30 yards (27.6 m.) in diameter has to be cleared to ground level; (*c*) a further 10 yards (9 m.) outside this circle must be cleared to within 2 ft. (60 cm.) of the ground and there must be no overhanging branches in this area which might foul the tail rotor; (*d*) a 30 degrees approach corridor must be prepared; (*e*) the centre of the clearing must be marked with towels or other suitable material to form the letter "H"; (*f*) areas of bad ground must be clearly defined so far as is possible; and (*g*) the patrols should use smoke to guide the aircraft to the clearing.

If there is a hospital within range the helicopter flies the patient direct there. When more than one patient has to be evacuated the helicopter ferries the cases to the nearest airstrip, and then Auster aircraft fly them on to hospital.

A Typical Sortie

To illustrate a typical evacuation sortie an extract is quoted from a report by the commander of the R.A.F. Casualty Air Evacuation Flight.

"The unit was informed that there were four British soldiers requiring helicopter evacuation from a position marked X on the Johore grid map. Taking off at 06.40 hours the helicopter landed at S—— at 08.50 hours. The flight was direct and uneventful apart from large patches of mist and broken low cloud. On arrival it was learnt that there were two stretcher and two sitting cases. The first stretcher patient had a bullet wound through his left groin, the second a bullet wound of his left ankle. The sitting cases were a Bren gunner who had a nasty palm wound which had nearly severed his left thumb, and a man with a flesh wound of the chest where a bullet had ricocheted off the bone near the heart. A casualty party consisting of a second lieutenant, a sergeant, and 30 men had left the main company and was proceeding to a clearing near the river at position X on the Johore grid, some 15 miles from S—— and about 24 hours' (plus) march away from transport facilities.

"Captain W. in an Auster took off at about 09.00 hours and after an hour's flying returned without finding the patrol. At 13.30 hours he took off again on another search and with no assistance from the ground patrol eventually located them in a small clearing at the river side. This was very fine work, as the patrol did not put up smoke or open up on the radio; in fact, Captain W. flew over the clearing once and assumed the men were tree stumps. The patrol actually arrived at this clearing at 13.20 hours. They stated that they had seen the Auster several times but did not put up smoke as it would slow their march. In the clearing they had thrown one smoke grenade but it failed to go off. Before sending the helicopter in to start the evacuation a further reconnaissance was made with a helicopter pilot in the Auster, Captain W. having reported that the clearing was perhaps too small. However, the clearing was considered to be of just the minimum requirements and the patrol were given instructions over the R.T. how to prepare the landing ground. The Auster then returned to S——.

"Take-off of the helicopter was delayed for 20 minutes because of a heavy rain-storm. It finally departed for the clearing at 15.15 hours, arriving at 15.30 hours. The clearing was in the middle of primary jungle surrounded by trees reaching up to 150 ft. (46 m.). The approach was slightly curved, but it was a good natural one owing to the height of the trees diminishing near the river. The centre of the landing ground was marked with towels. The first case to be evacuated was the patient with the bullet wound of the left groin. One pilot was left in the clearing to marshal the helicopter in 'turning on the spot' so that it could take off over the line of best approach and at the same time he could help to speed up loading. The helicopter then returned and picked up the second stretcher case. The patient with the nearly severed thumb was evacuated next. These three sorties between the clearing and the airstrip at S—— were accomplished in 75 minutes. The helicopter was then refuelled and returned for the last casualty. The operation was finally concluded after 105 minutes from the first take-off.

"The patient with the groin wound was the only one in pain, but the R.M.O. said the hand was the worst case. The Casualty Air Evacuation Flight offered to fly any of the patients to hospital at K——, but the R.M.O. declined. All the men left by road ambulance, after initial treatment, at approximately 17.30 hours. It can therefore be assumed that as K—— is only 35 miles away from S—— all patients were in hospital by 19.00 hours. All the casualties were national service men, and their patience and uncomplaining cheerful attitude were a credit to their regiment. During the flights from the clearing to S—— each patient's personal equipment was carried, and medical stores and mail were taken on the return trip. As it was too late to return to

base that night the aircraft was "D.I.'ed" (routine daily inspection) and the crew remained for the night at S——. In the morning the helicopter returned to base, refuelling at K——, as there were only 32 gallons (145 litres) of 100 octane remaining at S——."

Conclusion

There have been many similar sorties carried out in which the helicopter has undoubtedly saved life and limb. As further experience is gained the R.A.F. Casualty Air Evacuation Flight will no doubt be able to answer all the calls for casualty evacuation.

The helicopter is invaluable from the medical point of view and has again proved its worth in Korea, where the American Air Force has been picking up casualties from the front line. As these aircraft operate usually below 2,000 ft. (610 m.) there are no clinical contra-indications to flight. Any patient fit for movement by surface means can safely be evacuated. Designers in this country are now fully aware of the medical requirements in design in order that the aircraft may be used to the best effect for loading and carrying casualties. Even hooks in the cabin roof from which blood bottles may be hung have not been forgotten.

I wish to express my thanks to those officers of the Far East Air Force who have provided me with information and to the Director-General of Medical Services of the Royal Air Force for permission to publish this article.

NEWS FROM THE BRITISH ASSOCIATION MEETING

The one hundred and thirteenth annual meeting of the British Association was held in Edinburgh from August 8 to 15. It was a special occasion in several respects. Being held in the Festival year, it was in part a centenary meeting, the centenary of the Great Exhibition. On that account there was more of stocktaking than usual and, as an extension from that, of extrapolation into the future. Secondly, the Association had the Duke of Edinburgh as its president, as in 1859 was Prince Albert, whose suggestion had led to the Great Exhibition. And finally the meeting was three weeks earlier than usual on account of the Edinburgh Festival.

The president's address was on "The British Contribution to Science and Technology in the Past Hundred Years." Among his examples were the birth of modern surgery in Scotland with Simpson's discovery of the use of chloroform as an anaesthetic and Lister's antiseptic technique; the work of Manson as the father of tropical medicine; and the leading part taken by the British Commonwealth in the promotion of public and personal health services. He spoke also of some omissions: the screw micrometer, invented in Britain but produced earlier in Germany and the United States; the silicone* group of materials developed in Russia and the United States from basic work by Professor F. S. Kipping, of Nottingham; and, from Navy experience, of "apparatus . . . used operationally exactly as the inventor put it together, with all the resulting disadvantages in maintenance and efficient operation." He drew the conclusion that where scientific principles are known by all nations the advantages lie in the good design of equipment for practical use.

Among those who looked to the future, Sir CLAUDE GIBB, president of the Section of Engineering, felt little doubt that within the next fifty years the gas-turbine motor-car would be used to the exclusion of all others. The remaining problem was the efficient recovery of heat from the exhaust gases. He suggested also that large-scale railway electrification might well be hastened by the application of atomic energy, since to justify the high initial cost generation of electricity would need to be substantial. In the use of materials, Dr. F. D. RICHARDSON (Imperial College, London) said that metals hitherto regarded only as alloying elements were becoming of interest as possible bases for new systems of alloys. An example was the relatively light metal titanium. It had a specific gravity of 4.5, excellent resistance to corrosion by chloride solutions, and a tensile strength greater than that of mild steel. Large quantities of titanium ores were available, and, if large-scale extraction could be improved, a new and important industry would almost certainly grow up and would help to relieve other shortages.

*Organosilicon compounds with a wide variety of properties, the combination of heat-resistance and high electrical insulation being two of the most useful. See, for example, Hardy, D. V. N., *Endeavour*, 1947, **6**, 29.

Chemistry and Medicine

Sir CYRIL HINSHELWOOD (Oxford), in his presidential address to the Section of Chemistry, referred to the present dimly appearing discernment of chemical processes in the cell, with chemotherapy dependent on their selective influencing, and the possibility of deep-seated chemical intervention into processes which were now normally inviolate. What was dimly appearing included the mutually aided autosynthesis of protein and nucleic acid, changes in the proportions of enzymatic material in response to the changed reaction velocities imposed by various environments, and discontinuous modifications in the molecular pattern caused by radiations or the accidents of abnormal cell division. The division of the cell itself was imposed by a physico-chemical influence known as the scale-effect, and occurred without doubt in response to a physico-chemical stimulus. The growth of chemotherapy must be long and difficult, because as yet the rational chemical basis for much that was known was incomplete. Chemically induced mutations of cells were already known in a crude fashion, the influence of drugs on personality already exercised medicine and the law, and the day might well come when a conscious moulding of individuals and even of races would present problems of fearful fascination.

Recent work on the adrenocortical hormones was reviewed, with special reference to cortisone, by Professor G. F. MARRIAN (Edinburgh). As an addition to published information,† he stated that an announcement of the total synthesis of cortisone on the laboratory scale would soon be made. This was the opening contribution to a symposium on "Organic Chemistry in the Service of Medicine." The following speakers were Dr. F. L. ROSE (I.C.I., Ltd.) on antimalarials, and Dr. R. V. PITT-RIVERS (National Institute for Medical Research) on recent work on the thyroid gland.

Underdeveloped Areas

A full day was devoted by the Section of Geography to the types of surveys needed in underdeveloped areas, particularly in the Tropics. Professor L. DUDLEY STAMP (London) suggested that the examples of the groundnuts scheme in East Africa and the abortive poultry scheme in the Gambia showed that, apart from possible mismanagement, there was inadequate knowledge on which to base development schemes. A first step must be to record the existing use of land and to try to discover the reasons for its use or non-use. The World Land-Use Survey was a recently established voluntary organization under the auspices of the International Geographical Union. It was carrying out pilot surveys in parts of Nyasaland, the Gold Coast, Nigeria, Libya, Kenya, and Somaliland, including experiments on the use of material from surveys undertaken for other purposes—air photographs in particular. Dr. A. S. THOMAS (Nature Conservancy) enlarged on the types of preliminary surveys needed. Attention must be paid not only to soils, animals, and plants, but to existing farming practices. In many parts of Africa the best soils were on the tops of hills, not in the bottoms of valleys—hill-top villages, enforced by mosquitoes, having led to soil-enrichment by plant-ashes and food residues. The low fertility of many equatorial soils was now becoming more generally recognized; and, in

†*British Medical Journal*, 1951, **2**, 406.

relation to livestock, treading by cattle led to such compaction of the soil, in the absence of frost to break it up, that rain cannot penetrate, with the result that stall-feeding and migration were used in hot countries. Sir GEOFFREY EVANS (Economic Botanist, Kew) referred to the value of plants as soil-indicators, and to human factors. Dr. H. GREENE (Adviser on Tropical Soils, Rothamsted) spoke on recent aids to soil surveys. He concluded by saying that there were too few technically competent men at work, that intense nationalism within many underdeveloped areas had been a growing obstacle, and that the British policy of encouraging the nationals of underdeveloped countries to take an active and responsible share in the work of development should be maintained.

Rain, Cloud, and Smoke

The Section of Physics, with a distinguished meteorologist, Sir DAVID BRUNT, as president, had a number of papers on meteorological subjects. Mr. B. J. MASON (Imperial College, London) discussed the physics of rain-formation, including its artificial stimulation. After experiments in a number of countries on the "seeding" of cumulus clouds with either solid carbon dioxide (carbon dioxide snow) or with silver iodide crystals, which in form resemble those of ice, he described as a very recent development the discovery that the most efficient method is to spray the underside of a growing cloud with water droplets. The size of the droplets found to be most effective is intermediate between the droplets in a non-raining cloud and those of the finest drizzle. Their effect was to start a coagulation process. From seeding experiments in many countries it had been concluded that for a good chance of success the cloud-top must be cooled already to $-7°$ C., compared with $-10°$ to $-13°$ C. for natural rain formation. He was sceptical of the idea that the rainfall pattern could be altered over large areas by such methods, but saw a possible economic value in the prevention of crop-damage by hail through the premature release of rain from would-be hail-clouds, of which he described the physical characteristics. Mr. I. C. BROWNE (Cambridge) described the use of radar to study clouds directly overhead. The variations of echo intensity with height represented variations in raindrop diameter and in the number of drops in a given volume, while they also indicated whether ice-particles were present. Mr. R. WILSON (Royal Observatory, Edinburgh) had used the 36-inch (0.9 m.) reflecting telescope at his observatory to study the "blue sun" of September 26, 1950—a phenomenon caused by a smoke layer at 30,000–40,000 ft. (9,140–12,190 m.) altitude from forest fires in Alberta, Canada, three days previously. The smoke from these fires drifted over North America, across the North Atlantic, and thence across Europe. The investigation showed that the particles in the smoke layer were not blue but transparent, and that the individual particles were identical in size and constitution, an effect which was unusual in nature and difficult to produce in the laboratory. They were thought to have been oil globules produced by the distillation of wood in the forest fire.

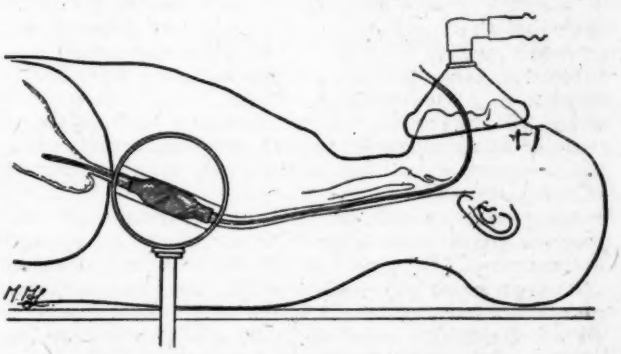
Extreme Environments

A joint session on life and work in extreme environmental conditions was held by the Sections of Physics and Physiology. Dr. O. G. EDHOLM (National Institute for Medical Research) gave a general account of physiological adjustments to temperature. Dr. F. MARSH (North-east Metropolitan Regional Hospital Board) described experiments on the response of the mammalian body at critical levels of hyperthermia, and Dr. N. H. MACKWORTH (Cambridge) on the performance of severely chilled hands. Signs of local acclimatization had been found in the hands of men who normally work outdoors in sub-arctic conditions, and further laboratory studies were being made. Dr. E. M. GLASER and Professor R. A. MCCANCE (Cambridge) gave a paper on body temperature and thermal balance. A balance between heat-production and heat-loss could be established under widely different conditions, with or without comfort, and at internal temperatures which might vary by as much as 3° C., and at skin temperatures which might vary very much more. Evidence of the connexion between working temperature and health efficiency and liability to accidents of workers was summarized by Dr. T. BEDFORD (London School of Hygiene and Tropical Medicine). A discussion on physiological problems of mining was opened by Dr. R. PASSMORE (Edinburgh) with a tribute to the pioneer work of Professor J. S. Haldane on the physiology of respiration and its practical applications to the safety of miners.

Preparations and Appliances

A CUFFED STOMACH TUBE

Professor R. R. MACINTOSH, Nuffield Professor of Anaesthetics in the University of Oxford, writes: Laryngeal spasm is not to blame for inadequate respiratory exchange after the use of curare, for the intrinsic muscles of the larynx are affected by the generalized paralysis and the airway through the cords remains free. If a mask is applied firmly to the face and air or other gases are pumped through it by squeezing the reservoir bag the lungs inflate easily; but with each squeeze of the bag a certain amount of gas is forced through the oesophagus into the stomach, which may become considerably distended. In order to obviate this I pass a stomach tube surrounded by an inflatable rubber cuff similar to that on endotracheal tubes. This cuff prevents gastric contents tracking up between the oesophagus and the tube in the well-curarized patient in whom the cardiac sphincter is relaxed.



The rubber cuff is placed 7 in. (17.5 cm.) from the distal end of the stomach tube. When the patient's reflexes are depressed a laryngoscope is inserted and the tip of the tube, well greased, is directed into the oesophagus. The laryngoscope is withdrawn and the tube advanced until—in an average adult—the tip is 18 in. (45 cm.) from the teeth. The cuff now lies in the lower end of the oesophagus. The proximal end of the tube is passed through a slit in the anaesthetic mask, and the cuff is lightly inflated with some 10 c.cm. of air. The stomach tube plays a part in keeping the tongue away from the posterior pharyngeal wall, but a metal airway can be inserted if required. The lungs can now be inflated easily without gas passing into the stomach, and stomach contents cannot reach the larynx.

Writing in the July, 1951, issue of *Science Progress* (vol. 39, p. 459) Mr. K. W. Keohane, of the Anatomy Department at Bristol, describes how long phase-contrast microscopy took to establish itself as a useful scientific technique. It was introduced by Zernicke in Holland as long ago as 1934, and soon afterwards demonstrated to biologists by Burch in England. At the end of a week's work Burch felt that their reaction was, "If they saw the same things using Phase Contrast as they saw using other methods, then there was no advantage in it, whilst if they saw anything different then the method was wrong." Since 1945, however, the new microscope has become an important research tool. This article explains the underlying theory.

Correspondence

Megacolon

SIR,—Your annotation (August 11, p. 346) makes it clear that we are now beginning to understand the totally different conditions hitherto lumped together under the name of megacolon. I hope it is not too late to suggest rational and intelligible names for them.

You divide these conditions into three groups, when in reality there is one single essential difference the recognition of which is the key to diagnosis and treatment. This point is whether the bowel is habitually over-active or habitually over-passive. The first condition shows violent visible peristalsis as the bowel attempts evacuation, is frequently fatal, and was quite intractable until Swenson performed the first recto-sigmoidectomy. There is no better name for it than that of Hirschsprung's disease, after the surgeon who first described it accurately.

The second group of cases has more varied primary causes than the absence of ganglia established by Bodian in Hirschsprung's disease, but the secondary effect is the same in all of them: a passive accumulation of faeces in the colon. Peristalsis is rare and slight, deaths are almost unknown, and persistent medical treatment is very successful. Now your annotation divides this group into two classes: (*a*) idiopathic megacolon, a name which, so far as I can understand it, means that the colon is enlarged because it has the idiosyncrasy of being enlarged; and (*b*) symptomatic megacolon, which suggests an enlarged colon which has the symptoms of being enlarged.

As all cases of enlarged colon whatever are both idiosyncratic and have the appropriate symptoms I see no sense in these names. For years now I have, in teaching, described the second group as *colonic inertia* on the grounds that its main characteristic is inertia of the colon. I then go on to classify the various causes which are idiopathic to each condition, and the symptoms which are symptomatic.

May I suggest that the term of megacolon be dropped entirely as only tending to confusion, and that in its place we speak of Hirschsprung's disease and colonic inertia? While I am on the subject of nomenclature I may note another term which I would be glad to see join megacolon in oblivion. It is the word naevus, employed in the excellent article (August 11, p. 348) by Dr. Hugh Gordon on "Cancer of the Skin." He uses it in the sense of a mole, whereas it is most commonly employed to mean an angioma, a totally different condition.

This insistence on the importance of nomenclature is not purely pedantic; for instance, the line of treatment suggested by misnaming a vaginal ectopic anus an "imperforate anus with recto-vaginal fistula" is responsible for the wrecking of many lives which might otherwise have been happy.—I am, etc.

London, W.1. DENIS BROWNE.

New Sign of Foetal Distress?

SIR,—I read Dr. G. I. Watson's letter (August 18, p. 417) with misgivings which I feel certain will be shared by others. It is not surprising that the plantar reflexes should become weaker and finally disappear in a dying foetus. But it is surely illogical to wrap the delivered part of a foetus in a warm towel (for which there can be no other indication than to protect it from thermic stimuli) and at the same time to stroke the sole of the foot "playfully" or for diagnostic purposes. We know from daily experience and from Sir Joseph Barcroft's classical experiments that cutaneous stimuli are potent factors in the initiation of respiratory movements. It is therefore earnestly to be hoped that there will be no place for a physical sign the elicitation of which is liable to produce the very condition one wishes to test for.—I am, etc.,

Bournemouth. NICHOLAS ALDERS.

SIR,—Dr. G. I. Watson's letter (August 18, p. 417) was very interesting. I cannot comment on his observation of the abolition of the plantar response as a sign of foetal asphyxia, but I can add another observation. Frequently while delivering a baby by the breech I have tested the plantar response out of idle curiosity. Whereas one would expect it to be extensor it is quite often flexor in type, to become extensor after the birth. This phenomenon seems unrelated to the condition of the baby and whether there are clinical signs of asphyxia, though I have not correlated it to observation on the pulsation of the cord.—I am, etc.,

London, W.1. KENNETH BOWES.

Twins Delivered after Death

SIR,—The following clinical note may be of interest.

A rather corpulent Chinese Hokkien woman aged 38 was admitted to the General Hospital, Malacca, at 9.30 a.m. on August 11. She was about full term pregnant and was said to be in labour. The previous history was of four normal deliveries, all boys, the youngest being 2 years old. On admission she was in a dying condition with acute cardiac failure, probably cardiac beriberi, knee-jerks absent. She died very shortly after admission and I was called at once.

She had been dead about five minutes when, without aseptic precautions, I opened the abdomen and uterus and delivered a living female child. A second child was then discovered, and after division of exceptionally tough membranes the second twin, also female, was delivered through the abdominal incision. Both infants suffered blue asphyxia, but after restorative measures revived, and at the time of writing (some three hours old) are both perfectly normal healthy newborn babies.

The history of the mother's illness, as is very usual in this country, is unreliable, but relatives say she was perfectly well 24 hours ago and became progressively dyspnoeic as labour continued. No post-mortem examination was permitted, and a provisional diagnosis of cause of death was made of cardiac beriberi.—I am, etc.,

Malacca. W. GLYN EVANS.

Diagnosis of Trypanosomiasis

SIR,—The memorandum by Drs. J. E. Cates and M. B. McIlroy (August 18, p. 401) well illustrates the fate which may befall a victim of trypanosomiasis while awaiting his diagnosis. But it is hardly correct to claim that the delay was due to failure of the established methods of diagnosis. From 1944 to 1950 it was known that an ex-soldier from the Gambia suffered from irregular pyrexia and cervical lymphadenitis, but there is no record of the accepted method of diagnosis—i.e., gland puncture—ever having been practised. Lymph nodes were excised in 1944 and 1948, and the authors rightly remark that there was nothing specific in the histological examination. But an examination of fresh gland juice would certainly have revealed living trypanosomes on at least one of the five occasions when the patient was admitted to St. Bartholomew's Hospital.—I am, etc.,

London, W.1. CLEMENT C. CHESTERMAN.

SIR,—I read with great interest the case report (August 18, p. 401) by Drs. J. E. Cates and M. B. McIlroy on the occurrence of trypanosomiasis in a British soldier. I appreciate the difficulties they encountered in establishing the final diagnosis, but am surprised that they apparently did not use one of the simplest methods of diagnosis—namely, direct microscopic examination of lymph-gland fluid after gland puncture. This method is of great value in carrying out field surveys of the incidence of the disease in endemic areas, and it is especially suitable in infection with *Trypanosoma gambiense*, where a large proportion of cases develop lymph-node enlargement.

I carried out such a survey in the Gambia in 1942–3, and found that by using this method alone the most effective case-discovery rate could be obtained. Medical officers who have dealt with trypanosomiasis in West Africa are familiar with the following technique, which was shown to me by Dr. G. Saunders, of Kintampo, Gold Coast.

A dry hypodermic needle with a short point is used. The selected lymph gland (usually cervical) is fixed between the thumb and forefinger of the left hand, and with the right hand the needle point is pushed through the skin into the substance of the gland. The needle is rotated once or twice on its axis, then withdrawn. There should now be a small quantity of gland "fluid" in the lumen of the needle. A dry 2-ml. hypodermic syringe with the piston partially withdrawn is now attached to the needle, and the contents of the needle ejected on to a microscope slide. It is not necessary to try to aspirate fluid from the gland with a syringe, as there is sufficient in the needle lumen for adequate examination. A tiny fragment of skin is usually found among the gland fluid, and it is important to flick this away with the point of the needle, otherwise the coverslip which is now applied will not sit properly and the preparation will be too thick. The skin fragment is very easy to see when the patient is an African, as it shows up as a black dot against the milky gland fluid. When the coverslip has been applied the slide is immediately examined under the medium power of the microscope, with the light partially cut down. If a trypanosome is present, it is usually quickly seen, as its appearance is very dramatic and never fails to produce a thrill of discovery. It behaves like a tiny hooked trout kicking and thrashing among the lymph cells.

I hope that this description of a very useful technique may be helpful to anyone who has trypanosomiasis in mind as a possible diagnosis in a patient from the West Coast of Africa. If lymph glands are enlarged, gland puncture should be one of the first diagnostic steps to be taken.—I am, etc.,

Weston-super-Mare. D. MCGOWAN.

SIR,—The report by Drs. J. E. Cates and M. B. McIlroy (August 18, p. 401) of a case of trypanosomiasis studied at St. Bartholomew's Hospital in 1947 and 1948 could not fail to recall to my memory a similar case seen in Winchester at about the same time. In this instance the same diagnostic error based upon clinical and biopsy evidence was made before the true character of the disease was suspected. In the Winchester case this suspicion was raised when a second opinion was sought on the histology presented in the cervical gland removed for biopsy. This suspicion resulted in a postponement of the irradiation which had already been prescribed but not started.

A 30-year-old motor engineer returned from West Africa in October, 1947. In March, 1948, he consulted his doctor on account of lethargy and some loss of weight due, as he thought, to two attacks of "malaria," from which he had suffered since leaving Africa. There was enlargement of all the superficial lymph nodes, those in the neck being most markedly involved. The spleen was enlarged so that its lower pole could be felt one hand's breadth below the left costal margin. Apart from a slight anaemia, there were no other abnormal findings. Save only for malaria while in Africa, there was nothing significant in his past history, and the family history was non-contributory.

There appeared to be little doubt that he was suffering from one of the reticuloses, and he was immediately admitted to hospital for further investigation. This included the removal of a cervical lymph node for examination. At this time, except for the presence of a secondary anaemia and an accelerated E.S.R., the tests carried out yielded negative results.

The appearance of the sections was not characteristic of lymphadenoma, and they were sent to Dr. Humphrey Gleave, of the Royal South Hants Hospital, Southampton, for a second opinion. It was with considerable surprise that I read his report, which recorded the possibility of trypanosomiasis and concluded with a request to know if the patient had ever been in West Africa.

Further investigation found an increase in the protein content of his C.S.F., which contained in addition 14 lymphocytes per ml. No parasites were demonstrated and the W.R. and gold sol curve were negative. Juice obtained from puncture of an enlarged gland showed trypanosomes in fair numbers. He was referred to the Hospital for Tropical Diseases, where the diagnosis was confirmed and a course of treatment with suramin was started. The patient made an excellent recovery, and when next seen in September, 1948, he was well. So far as I know there has been no recurrence of symptoms.

I note that Drs. Cates and McIlroy refer to the very few reports on the histology of the almost constant lymphadenopathy seen in trypanosomiasis. This would appear to make all the more remarkable the accuracy of Dr. Gleave's report in my case, more especially as he knew nothing of the man's past history. I have been encouraged to add this postscript to the interesting article published in the *Journal*, in the first place because trypanosomiasis is but rarely seen in this country, and because when it does crop up there seems every possibility of mistaking it for lymphadenoma; in the second place it would appear that histology as well as protozoology is able to suggest a correct diagnosis when gland biopsy is carried out during the investigation of such an illness.—I am, etc.,

Southampton. KENNETH ROBERTSON.

Toxic Effect of Proguanil

SIR,—Dr. Peter Abbott in his letter (August 18, p. 419) asks for views on the subject of the toxic effect of proguanil. After an extensive experience of the use of proguanil, both as a suppressive and curative, in malaria I was never able to prove any definite toxic effects. An occasional individual reported slight gastric disturbances, but in these cases the drug was nearly always found to have been taken on an empty stomach, and furthermore the subject was invariably a chronic sufferer from some form of helminth infection.—I am, etc.,

Co. Dublin. C. S. P. HAMILTON.

Future of Rheumatism

SIR,—The report on rheumatic disease from the Royal College of Physicians must be encouraging to the few physicians who have struggled to obtain recognition for this group of diseases, small in number but widespread in effect. In the past, men of the status of Heberden, Garrod, and Charcot, unquestionably general physicians, had an especial interest in chronic rheumatism. The fear experienced in your leading article (August 18, p. 408) that rheumatism may become a narrow specialty does not seem to be justified by the facts. Recent reports from the United States suggest that maintenance therapy with cortisone, sufficient to keep the patient ambulant, though often not entirely symptom-free, but insufficient to give serious side-effects, may be possible in some 60% of patients with rheumatoid arthritis. If further experience should confirm this, the rheumatism specialist of the future is likely to be using hormone therapy and, if cortisone can be produced more cheaply, using it on a large scale.

Be this as it may, the fact remains that all that presents at a rheumatism clinic is not rheumatism in the commonly accepted sense; a moment's reflection will call to mind many non-rheumatic conditions which may present with pain in, or referred to, the musculo-skeletal system. Whatever the future of hormonal therapy in rheumatism—and my belief is that it has a future—no physician worthy of his salt can close his eyes to a wide diagnostic spectrum when confronted by patients complaining of pain in almost any part of the body. It seems to me axiomatic that the specialist in rheumatism *must* be a general physician. This in my experience is certainly so in America, where most specialists in arthritis go "on service" in general medicine in addition to acting as consultants in their specialty, and also do general medicine in private practice. While the medical framework in this country is probably not sufficiently elastic to permit this kind of arrangement there is no reason why the future specialist in rheumatism should not work in one general out-patients a week, albeit in a subsidiary capacity, and attend the staff rounds and meetings of his teaching hospital centre. The foregoing does not take into account that the physician in charge of a rheumatism centre will be responsible for conducting and organizing research in his subject. It seems unnecessary to stress the knowledge of other fields, and the interplay and exchange of information with his colleague, required of the present-day clinical research worker.—I am, etc.,

London, W.12. G. R. FEARNLEY.

Social Conditions and Juvenile Rheumatism

SIR,—I am not sure what is meant by your editorial statement (July 21, p. 162) that "research into the social background of this disease [rheumatic fever] is important, though it has so far produced largely negative results." There are many sides to this question, but here I want to draw attention only to the highly satisfactory course in recent years of mortality from heart disease in children in England and Wales. Since the Registrar-General classifies deaths from congenital malformation separately, the "heart disease" which causes mortality at 5–15 years of age is, for all practical purposes, rheumatic.

Before the war this death rate was strongly associated with industrial and town life and, above all, with poverty.[1] Consider the figures for two regions with similar climates but very different social circumstances given in Table I.

TABLE I.—*Mortality from Heart Disease at 5–15, M. & F. Combined, per 100,000 Living, 1929–33*

England and Wales	Type of Area	(1) S.W. England	(2) S. Wales
13·4	County Boroughs	10·4	17·9
11·2	Urban Districts	7·6	20·1
7·9	"Rural" Districts	4·9	18·8
All—11·4			

Moreover, there were indications that this death rate was possibly even more sensitive to social conditions than infant mortality or the phthisis death rate in young women, and that it responded, though in a peculiar manner, to even short-term changes in such conditions, as measured by the level of unemployment.[2]

Lagging somewhat behind rheumatic fever, mortality from (rheumatic) heart disease began to fall about 1936 in the more prosperous parts of the country; and it therefore seems reasonable to inquire whether the rise in the standard of living of the wage-earning majority of the population during and since the war is reflected in the course of this death rate. In a previous investigation[3] the county boroughs of England and Wales were classified in 10 groups according to their experience of unemployment between 1927 and 1938. Group A towns suffered worst in the great depression of the 1930s, Group J least. In Table II are the relevant death rates for these towns, at the end of the depression and post-war.

TABLE II.—*Mortality from Heart Disease at 5–15, M. & F. Combined, per 100,000 Living*

Towns	(No.)	1936–9	*1946–9*
Group A	(7)	19·1	*5·7*
Group J	(9)	4·3	*3·0*
All England and Wales		8·7	*3·4*

As a result of this remarkable fall the number of deaths is now very small. It can be seen, however, that Group A towns still had a higher death rate in 1946–9 than Group J about 10 years before. But the Group A rate has fallen by 70%, compared with a fall of 30% in Group J, so that the extremes of mortality (which paralleled the extremes of unemployment) have disappeared. A social gradient remains, but the difference is less than half of what it was. (The South Wales figures for 1946–9 incidentally are: County Boroughs, 4.2; Urban Districts, 5.5; "Rural" Districts, 3.9, per 100,000.)

When a contemporary social index is used instead of one transposed from pre-war the results are similar. Chisholm and Hovey have recently[3] graded a large number of towns by income levels and purchasing power, and Mr. L. T. Wilkins has kindly revised these figures on our behalf for 66 county boroughs, to render them more suitable for socio-medical investigation. We intend to use this index for correlation with mortality and other rates, pending the publication of the local results of the Census. Meanwhile, they have been applied to (rheumatic) heart disease mortality as above. In Table III, Group 1 County Boroughs were the poorest in 1949–50, Group 4 the most prosperous.

TABLE III

Towns	(No.)	*1936–9*	1946–9
Group 1	(19)	*18·9*	5·5
Group 2	(20)	*12·2*	4·4
Group 3	(14)	*11·6*	3·6
Group 4	(13)	*7·8*	3·7

It is not possible to consider housing separately, but it is interesting that the decline has taken place in a period during which housing conditions have not improved.

As Glover[4] has pointed out, there are three sets of factors to be considered in interpreting such trends: (i) social and economic circumstances, including nutrition; (ii) the development of preventive services and of treatment; (iii) the "biological" factors associated, for instance, with Group A haemolytic streptococcal infection, and the responses to it; and so far it is not possible to add to these in the light of modern discoveries in rheumatic fever and allied conditions.[5] There have recently been movements in all three kinds of factor. What may be happening is a change in the streptococcal one mainly, though such changes have coincided in the past (as recently) with social change. The upshot may well be that we are reaching levels of mortality in the community at which individual constitutional influences are becoming increasingly important. And social as well as medical investigation will continue to be necessary if the contribution of these various factors, which have so changed the picture of this disease in little more than 10 years, is to be understood.—I am, etc.,

M.R.C. Social Medicine Research Unit, Willesden. J. N. MORRIS.

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"Mess Trick" and "Fainting Lark"

SIR,—Professor E. P. Sharpey-Schafer and his co-workers in their interesting paper (August 18, p. 382) say that the schoolboys "are to be congratulated on their ingenuity." Still more so are babies, for lots of babies learn this trick between the age of 6 and 18 months. The attacks, well known to every paediatrician, are called breath-holding attacks, the "kinks," or breath-holding convulsions. The babies cry for a variety of reasons and then hold the breath in full expiration, rapidly going limp, and very occasionally having an actual major convulsion.—I am, etc.,

Sheffield. R. S. ILLINGWORTH.

SIR,—The interesting article by Drs. P. Howard, G. L. Leathart, A. C. Dornhorst, and Professor E. P. Sharpey-Schafer (August 18, p. 382) on the physiology of the "Mess Trick" and "Fainting Lark" has prompted me to record the following observation.

Following radical excision of the breast for carcinoma and post-operative radiotherapy, a fair proportion of patients develop as a legacy a cumbersome oedematous arm, the treatment of which is never very satisfactory. In the course of routine follow-up examination a patient was found to have decreased the girth of her oedematous limb very considerably, and on questioning admitted, somewhat reluctantly, that she had consulted an osteopath. It was difficult to imagine what good an osteopath could do to relieve the swollen arm, but with some persuasion she described what amounted to the mess trick in the recumbent posture—the manœuvre being performed several times at each consultation.

Her two complaints were bruised ribs and an empty purse, but her praises were for the dramatic way in which her swollen arm was reduced. At the time insufficient thought was given to a physiological explanation of this phenomenon and the matter shelved.

In the light of the article, however, it is conceivable that the two physiological mechanisms combine to allow the return of some of the accumulated oedema by way of the veins. As I see it, this will occur when the venous pressure is lower than the oedematous tissue pressure. Perhaps the unsung osteopath was right in performing the manœuvre frequently at subfainting levels—certainly he knew the right approach to his patient.

So far the opportunity of investigating this problem further has not presented itself, but it will, and success would be more impressive than a collection of interesting kymograph tracings, however valuable they may be.—I am, etc.,

Edinburgh, 4. W. D. RIDER.

Penalties for Sexual Offences

SIR,—Dr. G. W. Fleming (August 11, p. 363) is indignant because a man of some standing and education has been sent to prison for 18 months for improper offences against five boys between the ages of 13 and 15. He considers that the penalty is out of all proportion to the crime. Let him think again. If the person in question had assaulted five girls of the same age, the penalty would surely have been very much heavier. The apologists for the homosexual pervert appear to assume that his sexual desire is so overpowering that he has no control over it whatsoever. That is quite wrong. There are good and bad homosexuals, just as there are good and bad among normally sexed people. Any practitioner of experience has come across men in his practice who are naturally homosexual in their desires but, being persons of high character, keep the same control over themselves as do heterosexual persons who have to lead celibate lives. I have had to deal with some of the unfortunate boys and their parents who have been the victims in similar cases to the one quoted by your correspondent, and the mental damage and distress is deep and lasting. It is no light crime. In my experience, comparatively few of these perverts take any steps to get cured, but let their desires become their ruling passion, as is the case of the ordinary voluptuary.—I am, etc.,

Hereford. H. WARD-SMITH.

Confinements in Hospital?

SIR,—I have recently received a copy of a memorandum from the Ministry of Health relating to selection of maternity cases for admission to hospital. It advises me that most multiparae who have had four or more children should unquestionably require admission to hospital for their confinements on medical grounds.

The dangers of multiparity are certainly well recognized. According to Munro Kerr (*Maternal Mortality and Morbidity*, Edinburgh, 1933) the maternal mortality after the eighth pregnancy equals or exceeds that for the primigravida, while the *Report of Maternal Mortality* (H.M.S.O., 1937) gives a similar result for the eighth and ninth pregnancy. It would seem, however, that there is considerable difference between the "grande multipara" whose uterus is worn out with much child-bearing and the woman who has had five or six pregnancies which may have been well spaced. There are undoubtedly complications such as accidental haemorrhage which are found principally in the multiparous patient, but these are not to be prevented merely by making arrangements for a hospital confinement. There is also the obvious fact that many multiparous women deliver themselves so easily as to have very little warning of the approach of parturition, and the advice of the memorandum quoted above is surely liable to lead to a large number of babies being born in ambulances and other undesirable places.—I am, etc.,

Birmingham. W. G. MILLS.

POINTS FROM LETTERS

Distribution of Chicken-pox Rash

Dr. W. EDWARDS (Ashtead, Surrey) writes: During a recent chicken-pox epidemic I saw a boy whose rash on the first day was confined to the area of the left deltoid, on which he had a fine crop. It was 24 hours before it spread to the rest of the body. I commented to the mother on this unusual phenomenon, and she wondered if it could be connected with his being immunized against diphtheria in the left deltoid region a week previously.

Exercise for the Over-40s

Dr. W. H. EDGAR (Alverstoke, Hants) writes: May I support Dr. M. E. M. Herford's letter (August 4, p. 299) on the importance of breathing? Probably the chief importance of games is that they enforce vigorous breathing. But when the age for games is past breathing becomes a neglected art. The best exercise those over 40 can take is to do three minutes' breathing exercise twice a day. This is best done by one minute's thoracic breathing—i.e., expanding the chest—then one minute's abdominal breathing—i.e., protruding and retracting the abdomen—finishing up with one minute's general breathing—i.e., completely natural deep breathing. The "massage" effect on the thoracic and abdominal viscera is most salutary, and incidentally it is probably the best way to avoid "parade fainting."

Blackcurrant Tart after Gastrectomy

Mr. E. WILSON HALL (Eastbourne) writes: May I put in a plea to the many surgeons who are these days doing partial gastrectomies on patients and sending them to convalescent homes, not to give instructions to their patients that they can have in future a full diet? The discretion of a patient cannot always be relied upon, and this week-end I have had two partial gastrectomy patients in very acute pain; one had eaten spaghetti and cheese followed by raspberries, and the other had had quantities of pastry in a blackcurrant tart. I have found in dozens of cases that these patients very often prefer to go on to a full gastric diet, where their food is more easily supervised by the sister in charge, and I make this plea for the benefit of the patients.

Pyrexia of Unusual Origin

Dr. A. DUFF (Salisbury) writes: Dr. J. W. Laws (July 21, p. 157) deserves the thanks of laboratory workers for showing how an error might have been avoided. . . The diagnosis is clearly what your scholarly contemporary has named "Munchausen's syndrome," with serum sickness, abscesses, and possibly homologous serum jaundice as concomitants. . . . I can recall a pyrexophilic Munchausen, a nurse, who was accustomed to give herself protein shock by means of milk injections, and who acquired a *Br. abortus* infection in so doing.

Absence of Appendix

Dr. J. R. F. E. JENKINS (Abergavenny) writes: I would like to refer Mr. A. L. Deacon (July 14, p. 116), your surgical authority (May 26, p. 1215), and correspondents requiring information on this subject to the *Medical Press* (February 12, 1947), wherein I dealt very fully with the many causes which are likely to lead incorrectly to such a conclusion, often with disastrous consequences. The article in question was headed "The Intramural Appendix," as I believe this to be the most common cause of the apparent absence of the appendix at operation.

Corrections

Under "Medical Education at Oxford and Cambridge" (August 25, p. 478) we stated that "the new regulations for the final M.B. examination are now in operation, with latitude for the taking of the examination under the old regulations for all who matriculated before October, 1946." This date should have been October, 1948.

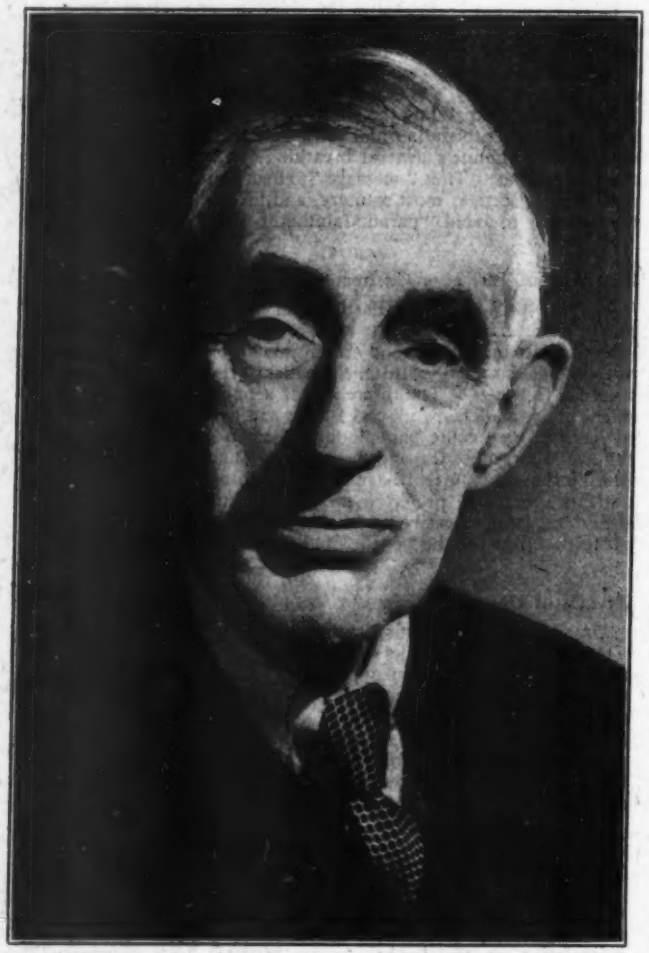
We stated in error (August 25, p. 492) that Birmingham awards a degree of Bachelor of Science in Public Health: this has never been the case and is not contemplated.

In the article on "Trichomonas Vaginalis Infections Treated with Penotrane" (August 25, p. 452) the strength of the pessaries should read "0.02%," not 0.2% as printed.

Obituary

G. GREY TURNER, M.S., LL.D.(Hon.), D.Ch.(Hon.), F.R.C.S.

We announce with regret the death on August 24 of Professor G. Grey Turner, the distinguished surgeon. He was emeritus professor of surgery in the University of Durham, consulting surgeon to the Royal Victoria Infirmary, Newcastle-upon-Tyne, and until recently professor of surgery in the University of London and director of the Department of Surgery in the British



Postgraduate Medical School. Professor Grey Turner, whose fame was world-wide, was in the best sense of the term a general surgeon with wide interests, and possessed a skill which enabled him successfully to perform operations of such difficulty as might deter those of lesser skill and courage. His career followed two paths. The first and longer was that in which he made his reputation and gave such wonderful service to the Royal Victoria Infirmary at Newcastle; the second was when he came to London as professor of surgery at the newly founded Postgraduate School at Hammersmith, where his operative skill and power of imparting knowledge brought men from all over the world to sit at his feet.

George Grey Turner was born at North Shields in 1877. He received his education at Durham University, where he graduated M.B., B.S. in 1898, and took the M.S. with first-class honours in 1901. After being house-surgeon at the Royal Victoria Infirmary, Newcastle-upon-Tyne, he filled the posts of demonstrator of anatomy and surgical registrar at the same hospital. There he came under the stimulating and inspiring influence of Rutherford Morison, who recognized his outstanding ability and chose him as his private assistant. This was the time when many operations were performed in the patient's home, and no doubt Grey Turner was thereby helped to develop that essential simplicity and trustworthiness of technique which was one of his characteristics. In 1906 he was elected to the staff of the Royal Infirmary, where his skill, daring, and extraordinary capacity for work soon brought him a high reputation and a large private practice. In the first world war he served for a time as consulting surgeon in Mesopotamia.

From an early date in his surgical career he took every opportunity of visiting foreign surgical clinics, and he thus became acquainted with the international figures in surgery and himself became known and recognized as a surgeon of great skill. When the Mayos visited Newcastle they particularly remarked on Grey Turner's dexterity and watched his work with interest. In 1927 he was made professor of surgery in the University of Durham, and in the following year his commanding position was recognized by his being chosen president of the Association of Surgeons of Great Britain and Ireland. Soon after this, in 1930, he delivered the John B. Murphy Oration in Philadelphia, and in the following year at Boston was awarded the Bigelow Medal for advancement in surgery. At a later date he delivered the Macewen Memorial Lecture in Glasgow and the Donald Balfour Lecture in Toronto.

At a time of life when most men would have been thinking of a well-earned retirement Grey Turner accepted the offer of the newly formed chair of surgery at the British Postgraduate School at Hammersmith. His vast experience and receptive mind, and his adaptability and gift of teaching, combined to make his new professoriate a great success; there for 12 years he taught several generations of postgraduate students from his wealth of surgical wisdom. Because of the war he continued to act as professor until he was in his seventieth year, and to the end of that time he still maintained his almost boyish enthusiasm for everything connected with surgery.

Grey Turner's association with the Royal College of Surgeons was spread over many years. He was a Hunterian Professor in 1928, and was elected to the council of the College in 1926, serving in that capacity for 24 years. He delivered the Bradshaw Lecture in 1935 and was Hunterian Orator in 1945, and was made vice-president of the College in 1937. The museum of the College was one of his special interests, and at one time he acted as chairman of the Museum Committee. After the museum was wrecked by bombing in May, 1941, he was energetic in helping to salvage what remained, though himself recovering from an operation. Many of the museum's treasures found safety in his own house until the end of the war.

Always taking an active interest in the work of the British Medical Association, he served as secretary of the Section of Surgery at Newcastle in 1921, as vice-president of the Surgical Section at Glasgow in 1922, and as president of the Surgical Section at Bournemouth in 1934. On coming to London he was active in the work of the Royal Society of Medicine, being elected

president in turn of its proctological and the general surgical sections. He was a Fellow of the Medical Society of London, in connexion with which Society he was appointed orator in 1929, and Lettsomian Lecturer in 1939, while in 1943 he served as president of the Society. In 1939 he went out on behalf of the British Council to Argentina and was actually there at the outbreak of war, but he managed to return home without mishap. He was a keen member of the International Society of Surgery, and was at one time its president; the success of the meeting of that Society in London in 1947 was largely due to his enthusiasm. His international reputation brought him honorary Fellowships or Memberships of medical or surgical societies in Sweden, Italy, France, Australia, and the United States of America. He was an Honorary Fellow of the American College of Surgeons, of the Royal Australasian College, and of the Edinburgh College. His own university conferred on him the honorary degree of D.Ch., and Glasgow the LL.D.

Grey Turner was a ready speaker and writer, and he published many articles on a variety of subjects. He edited Carson's *Modern Operative Surgery* after the first edition, and contributed to various "systems of surgery" and to surgical journals. In the issue of this *Journal* devoted to "Fifty Years of Medicine" (January 7, 1950) he contributed a lively account of "Surgery in 1900." From his private collection he lent this *Journal* the photograph of Rutherford Morison operating which was reproduced in the same number.

As a man, Grey Turner was even-tempered, tolerant, always eager to learn any new fact or technique, and willing and anxious to help anyone who came to him for assistance. He did not care for display of any kind, and in appraising his own work showed a self-criticism that is all too seldom seen. His surgical technique was sure and safe, and his results were accordingly remarkably good. He was very conscientious—a quality which was well shown during the war of 1939–45, when he opposed the slightest relaxation from the strict carrying out of the war restrictions. Like Gladstone, whenever possible he preferred to send a postcard rather than a letter. Over the years he was a constant adviser and friendly critic of this *Journal*. When asked for help he would go to endless trouble in giving it, down to the smallest detail. He kept in communication with many of his surgical friends abroad, and his office at Hammersmith was decorated by very many of their photographs.

Grey Turner's interests were not entirely confined to surgery. He was a member of the Barbers Company and a Freeman of the City of London. He took an interest in archaeology, and used to delight in conducting parties of his friends along the Roman Wall which was so near to Newcastle. No mere technician, he was a professional man in the fullest sense of the term, and by his integrity and example exerted a profound influence on the many younger men who came into contact with him. He lived a full life, and will long be remembered as one of the most distinguished surgeons of his time.

In 1908 Grey Turner married Alice Grey, B.Sc., daughter of F. E. Schofield, J.P. There were four children, three daughters and one son, who is an Assistant Secretary of the British Medical Association.

A memorial service will be held at the Church of St. Bartholomew-the-Less on Monday, September 3, at noon.

We are indebted to Sir GORDON GORDON-TAYLOR for the following appreciation:

The death of George Grey Turner has removed from our midst an international surgical figure, a master surgeon respected and beloved wherever surgery is practised throughout the world. Those who have been reckoned great in surgery must of necessity be supremely skilled in the craftsmanship of their profession; they must by reason of the initiation of some novel and successful system of treatment or by the inauguration of some policy have conferred some material benefit on mankind; their work must have illumined the dark, mysterious chasms in our knowledge of disease. It is necessary that they should have inspired their pupils and their surgical brethren with their own ideals. How truly he fulfilled these criteria of surgical greatness! In his halcyon days in Newcastle-upon-Tyne his operating theatre was a veritable Mecca for every pilgrim surgeon from transatlantic shores or from across the Channel or the North Sea, as had been Moynihan's theatre in Leeds a decade before; and during his London period of surgical activity "G.G.T." was still a powerful lodestone attracting surgeons to the new "set-up" at Hammersmith. He was never the Herrick among operators that Moynihan was with his lovely, flawless artistry. His success as an operating surgeon came from a natural ability with his hands, his profound judgment, and his vast experience—I doubt if any surgeon of our land has ever boasted an experience comparable with his.

Grey Turner was no specialist, yet he excelled in those very surgical procedures which to-day are the province of the specialist: his activities ranged from the treatment of cleft palate to the mundane bunion or the miner's semilunar cartilage. An abiding interest was the surgery of congenital malformations of the bladder and external genitalia, and dozens of cases of ectopia vesicae were transformed by his skill in uretero-colonic transplantation into clean and decent humanity.

No surgeon has done more than Grey Turner by precept or practice to encourage a bold front in the treatment of malignant disease. His *Encouragements in Cancer Surgery*, written more than twenty-five years ago, should be read by every young surgeon. His oration before the Medical Society of London twenty years past, which dealt with cancer of the colon, not only revealed the enormous wealth of his own experience, but did much to encourage surgeons in the ablation of colonic neoplasms which had already implicated the abdominal parietes or other viscera. His Harveian Lecture to the Harveian Society entitled "Nil Desperandum" was indeed a message of courage and hope.

No one, save perhaps W. R. Douglas of Manchester, can have had his experience of "block dissection" of the neck in cases of cancer of the oral cavity; certainly no one can have performed the operation with greater thoroughness, assurance, or speed. In his Newcastle days he was a vigorous champion of the perineal excision (Hochenegg) of the rectum in suitable cases; the perineo-abdominal extirpation now in vogue with some operators derived its origin from the extended operation which he practised in those cases where the perineal operation alone did not afford the extensive ablation of tissue which he desired.

Perhaps his greatest contribution to the advancement of surgery was his pioneer work in the treatment of the cancerous gullet. He was awarded the Bigelow Medal by the Surgical Society of Boston, U.S.A., in 1931—the only Englishman to receive this honour—and he chose

the surgery of the oesophagus as the subject of his Bigelow Lecture.

> "Who, not content that former worth stand fast,
> Looks forward, persevering to the last,
> From well to better, daily self-surpast."

His first successful extirpation of a carcinomatous oesophagus was not to come till 1933, the *annus mirabilis* in the history of oesophageal surgery in Britain.

Throughout his life Grey Turner was diligent with his pen, and his great experience commanded the profound respect and attention of his audience in any surgical discussion in which he chose to participate. Reference to the Cumulative Index attests the industry of his pen. Alas, he was not spared to see the Fourth Edition of *Modern Operative Surgery* on the booksellers' shelves. He was never a daimonic force that could resurrect some fallen temple or swing the trend of medical politics into a new orbit. The present epoch in medical affairs demanded a more Cyclopean leadership than his: he was a master surgeon, not a juggler face to face with a recalcitrant governmental Ministry. He had an insatiable love of museums, and was well acquainted with most of the pathological storehouses of the world. No surgeon has possessed such a knowledge of morbid anatomy, and, as he told us in his Hunterian Oration, the desire to collect was almost inborn in him.

Of those who had influenced him most he venerated Bland-Sutton and never tired of quoting him, frequently imitating the latter's quaint mode of speech. The life story of Sir James Paget exerted a profound impression on him: as befitted one who had received the honour of a Perpetual Studentship at "Bart's," he lectured on the "Paget Tradition" in the United States, and many of the passages quoted from Paget's addresses might well have applied to himself: "The burden of my address is work, lifelong work. And so it is, and so it will be: there is no success without it." But indubitably Rutherford Morison did most to mould and direct his early surgery. He admits himself that the sunlight of their friendship would at rare intervals be clouded over by evanescent nebulae; nevertheless he was chosen in 1947 to deliver the first Rutherford Morison Lecture within the walls of the "R.V.I.," where thirty years before he had made the presentation address to his old chief on the occasion of the unveiling of a medallion in bronze, a tribute from his old house-surgeons. The third edition of *Modern Operative Surgery* was dedicated to Morison's memory.

Grey Turner's own pupil surgeons were legion, but of all perhaps Lambert Rogers was the disciple he loved most—or was it Norman Hodgson? There were myriads of others—Franklin of "The Postgraduate" and Douglas, now of St. Andrews, and all the Newcastle group, including specialists like George Mason and J. I. M. Black. In retrospect the long years of friendship present a kaleidoscopic vista: the hospitable home at Jesmond; the topiary at beautiful Huntercombe Manor; the wards at the R.V.I., packed with extra beds to twice their capacity, with frenzied sisters loyally abetting him; the operating sessions on a Saturday from 9.30 a.m. till 5 p.m.; the surgeon with his Wellingtons having his frugal lunch of a boiled egg and the blackest brew of tea; the lantern lectures in the alleyway outside the theatre; the slide of Bassini—"Bassini's operation has produced the best results in the hands of the greatest number of surgeons." In the theatre complete sang-froid, absolute self-assurance, and the unerring skill with which, by means of angled scissors and a few bold, deft snips, he would separate rectum from vagina along the recto-vaginal septum without "holing" either. There were the clinical demonstrations too. Did any surgeon ever inspire such confidence, such complete and absolute confidence? And there were the old patients: the old fellow with his own lower jaw in a bottle in one hand and his rectum in the other; he is dead now like the surgeon who twice saved him, but he survived more than twenty years (many a half-crown nimbly pressed into his hand by his surgeon went into the till in the tavern by the bridge over the Tyne). Was any surgeon ever so worshipped by his patients? If he ventured to walk the street with that characteristic gait of his, bowler hat seemingly too big and perched on the back of his head, his progress would be constantly stopped by those who were his devoted patients. He remembered them all: their personal troubles, the number of mouths to feed, the number of days at work when times were bad—the ready sympathy always there, so genuine. How it helped! Some of his own personal foibles endeared him the more to his friends and compel a smile even at this moment of poignant grief: the frequent postcard with some comment or reminder, the much-used and readdressed envelope, the claim for his septuagenarian ration of tea!

The first great war took him to Mesopotamia, where he acted as consulting surgeon in the Amara District, and in the late summer of 1918 he was a member of a surgical mission to the U.S.A. comprising Duval, Bastianelli, Gask, and himself. There he dealt especially with the end-results of chest injuries, uttering a plea for pulmonary decortication, which had a considerable vogue in the second world war. He readily took the place of Tudor Edwards, whom illness debarred from undertaking a surgical mission to Latin America shortly before the outbreak of war in 1939, at a time when it was deemed highly important to advertise British surgical achievement in a continent where our reputation in this realm was indeed nugatory. In this mission he was greatly helped by his devoted wife, whose linguistic talents were to stand him in good stead. The storm clouds of war had burst on Europe before he returned.

He had been a prominent member of the council of the International Society of Surgery since its inception, and in 1949 was President of the XIIIth Congress of the Society at New Orleans. He was the second Briton on whose shoulders this honour had fallen. His name is perpetuated with the world's international surgeons of the century: Kocher and Czerny, Depage and Keen, Macewen, Hartmann, and de Quervain; Schoemaker of the Hague, and his own beloved friend, Matas of New Orleans; Leopold Mayer and René Leriche. He was numbered now among the world's surgical immortals, but I believe that the award of the Honorary Fellowship of the Royal College of Surgeons of Edinburgh, which was conferred on him only three months ago, delighted him most of all. To have been associated on this occasion with my old friend to whom I owe so much is indeed for me a cherished memory.

He came to London late, and, though a Freeman of the City of London, he was never really of London; his roots were in his beloved Tyneside, and he remained a true Northumbrian to the end. Perhaps the closing words of his Hunterian Oration form his truest epitaph: "A spirit communicated is a perpetual possession." But I know that there must be many who will say with me, perhaps under their breath, as they wistfully think of this great master surgeon of international reputation, such words as these: *De republica bene merebatur, sed ille maestus honoribus dignis indignissime carebat.*

L. C. R. writes: Others will speak and write of Grey Turner's leadership of British surgery and the distinctions he achieved in it, his careful sound work, his enthusiasm in the fight against cancer and against infection, his inspiring influence on young men, his interest in the history of his subject and of the things of the past, but I would pay tribute to him as a man and as one who loved and served his fellow men.

George Grey Turner—the Professor, as he was known to so many of his younger friends—was a simple man of simple tastes, who lived, dressed, and ate simply. He had the simplicity of true greatness. He was always attired in the same way and wore the same type of hat—a bowler—except on a famous occasion, the meeting of the International Society of Surgery in London in 1947, when he astonished and delighted his friends by appearing in a broad-brimmed panama type of straw hat. There was absolutely no viciousness in him, and I never heard him say an unkind thing of anyone—at the very worst he might say something like, "So-and-so is a little too brilliant for a young man," and even this was said kindly—and he was a shrewd judge of character. Outside his profession he had few interests that were unconnected with it; he loved to walk in his garden and talk to his friends, especially of surgery and its great masters. He rarely visited places of entertainment, but he liked travelling. Although you rarely found him reading anything outside his subject or an occasional newspaper, he was always well informed on matters of general interest and world affairs. His knowledge of surgery was encyclopaedic, and rarely, if ever, could one consult him about something to do with the subject without receiving the information sought. He was a great worker, with great respect for the unforgiving minute, and drove himself hard right to the end. When seized with the fatal illness he was hard at work completing a new edition of his *Modern Operative Surgery*. Above all he had a great attraction for young men which endeared them to him and him to them. Like John Hunter, he was "the dear man" to his friends and colleagues. Loving our profession, he was content to work in it and for it in a way that few have done in recent times.

ALEXANDER MACLEAN, M.D., D.P.H.

Dr. Alexander Maclean, chief supervisory tuberculosis physician to the Glasgow area of the Scottish Western Regional Hospital Board, has died at the early age of 45. He was a native of Islay, and studied medicine at the University of Glasgow, from which he graduated M.B., Ch.B. with commendation in 1929. He took the Diploma in Public Health in 1932 and proceeded M.D. in 1936.

Professor Charles Cameron writes: Maclean's introduction to public health came with his appointment as assistant physician to the County Fever Hospital, Motherwell, where he worked under Dr. John Reid, and he became subsequently senior assistant physician to Ruchill Fever Hospital, Glasgow. From there he passed as clinical medical officer to the Public Health Department of the Corporation of Glasgow. Much of the work in this post was related to tuberculosis and included the directorship of the mass radiography unit. When in 1945 Dr. Stuart Laidlaw became medical officer of health of the city, Maclean succeeded him as senior tuberculosis officer, a position which he held until 1949, when he received his appointment from the regional board. Maclean's training had fitted him admirably for this work, which he tackled with vigour and enthusiasm. The tuberculosis problem in Glasgow had always been serious. The war years had added their increment, and it was no light burden which he accepted. Inadequacy of staff and shortage of beds were part of the problem, and it is not generally known that Maclean was a pioneer in the domiciliary treatment of tuberculous patients by the simpler collapse measures. His establishment of a streptomycin centre for out-patients was perhaps more debatable, but it was part of his vigorous reaction to the growing difficulties.

A member of the Tuberculosis Society of Scotland, Maclean was for many years its honorary secretary. He was lecturer in clinical tuberculosis to the University of Glasgow and was a member of the Committee on Tuberculosis of the Scottish Health Services Council set up in July, 1948, by the Secretary of State for Scotland. He supplied to that committee many statistics on housing, overcrowding, and other matters affecting the problems which came before it, and he played an important part in the drafting of the final report.

He was a hard-working man, and his staff worked loyally with him. He was reticent about his own health, but those who knew him were aware that his large frame covered some weakness. He carried on energetically until a complete physical breakdown came at the end of 1950. He recovered partially from a grave illness and his ultimate death was not unexpected. Maclean was a cheerful colleague, made excitable at times by his physical ailment, which was also responsible for an apparent tactlessness which alienated many; but he was a kindly, willing, and helpful man, and he leaves behind him a record of responsibility and honest endeavour. The tuberculosis world is the poorer for his passing and there are many who feel sympathy for his wife and daughter.

Dr. NORMAN JENNINGS, Hull City Coroner for 16 years, died suddenly at the age of 60 on August 7. Dr. Jennings was born at Cockermouth, Cumberland, and was educated at Carlisle Grammar School. He graduated at Edinburgh University in 1916 with the degrees of M.B., Ch.B. He was called to the Bar in 1931, becoming a member of the Inner Temple, but never practised as a barrister. During the first world war he served as a temporary surgeon in the Royal Navy. After a short period at Bradford he went into general practice at Hull in 1920. He was surgeon to Hull Trinity House from 1927 and was appointed police surgeon to the Western Division in 1931. In 1935 he succeeded Dr. John Durne as coroner. He was chairman of the local medical committee and a member of the local executive council of the National Health Service. For over 30 years he was an ardent supporter of the St. John Ambulance Brigade, of which he was a County Commissioner until this year. A life member of the St. John Ambulance Association, as an examiner he played a large part in its competitions. He was a Commander Brother of the Order of St. John and vice-chairman of the St. John Council. Dr. Jennings was a man of wide and varied interests. He was greatly loved by his patients, and as a coroner was held in high esteem by the medical profession and the lay public. He was forthright in manner and outspoken and uncompromising in his judgments, which were nevertheless fair and impartial. His hobbies were fishing and shooting. Despite his arduous duties as coroner, general practitioner, and police surgeon, he still devoted much of his time to furthering the interests of general practitioners in the National Health Service. Dr. Jennings leaves a widow, one son, and two daughters, of whom the son and one daughter are practising medicine.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the week ending August 11 (No. 32).

Figures of notified *cases* are for: (*a*) England and Wales (London included). (*b*) London (administrative county). (*c*) Scotland. (*d*) Northern Ireland. (*e*) Eire. Figures of *births and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included). (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland. (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

Disease	1951 Week Ending August 11					1950 Corresponding Week					1942–50 England & Wales Corresponding Week		
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	Highest	Median	Lowest
Diphtheria	19	—	5	1	2	49	5	12	3	1	656	243	49
Deaths	1	—	—	—	—	—	—	—	—	—			
Dysentery	149	25	75	—		211	9	80	—	—	300	107	51
Deaths		—		—			—		—				
Encephalitis, acute	6	—	—	—		9	—	—	—		9	2	—
Deaths		—			—		—			—			
Erysipelas			20	2	2			13	1	2			
Food-poisoning	77	12		3		225	15		—				
Infective enteritis or diarrhoea under 2 years				10	70					32			
Deaths	7			1	—	14		2	—	2			
Measles*	3,621	69	74	128	83	6,420	474	90	54	149	6,420	3,299	1,485
Deaths		—	—	—	—			1	—	1			
Meningococcal infection	24	—	15	2		21	1	19	—	2	74	38	21
Deaths		—	—				1	—					
Ophthalmia neonatorum	25	2	8	—		37	1	23	—	—	108	66	37
Pneumonia, influenzal	221	7	3	3		256	14	1	2		440	282	225
Deaths (from influenza)†	4	1	—	—	—	7	—	—	—	1			
Pneumonia, primary			94					109					
Deaths	127	19		4	4	135	26		5	3			
Poliomyelitis, acute:													
Paralytic	55	4	} 10	} 1	} 1	} 392	} 25	} 58	} 16	} 3	} 624	} 19	} 10
Non-paralytic	57	1											
Deaths§	1	—			—	23	—			—			
Puerperal fever			6				—	7					
Puerperal pyrexia‖	189	18	11	1	2	93	4	7	—	1	175	116	88
Scarlet fever	468	33	75	5	17	695	27	96	48	49	1,597	774	680
Deaths		—	—	—	—			—	—	—			
Smallpox	—	—	—	—		—	—	—	—	—			
Deaths				—					—	—			
(1) Tuberculosis, respiratory			126	20				124	25				
(2) Tuberculosis, non-respiratory			27	1				19	1				
(1) Deaths	} 117	{ 17	12	5	8	} 117	{ 12	18	3	6			
(2) Deaths		{ 3	3	—	1		{ 2	3	1	2			
Typhoid fever	12	2	3	—	1	5	—	3	1	1			
Deaths¶	—		—	—		—	—	—	—				
Paratyphoid fever	44	7	5 (B)	1		2	—	—	—	1 (B)	102	20	7
Whooping-cough	2,661	135	335	74	74	3,422	253	256	21	54	3,458	1,738	936
Deaths	2	—	—	1	—	4	—	1	—	1			
Deaths (0–1 year)	173	23	31	15	18	191	20	28	8	24	328	278	191
Deaths (excluding stillbirths)	3,646	543	494	83	144	3,963	577	503	91	145	3,972	3,663	3,577
Annual death rate (per 1,000 persons living)			10·1					10·1					
Live births	6,712	1,036	855	245	329	6,627	1,094	863	228	386	8,373	6,627	5,919
Annual rate per 1,000 persons living			17·5					17·3					
Stillbirths	184	20	24			167	12	19			261	197	167
Rate per 1,000 total births (including stillborn)			27					22					

* Measles not notifiable in Scotland and returns are approximate. † Includes primary form for England and Wales, London, and N. Ireland. § The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

Vital Statistics

Births and Fertility in 1949

The birth rate in England and Wales in 1949 was 16.7 per 1,000 population, and there were 730,518 live births (Registrar-General's *Statistical Review, 1949, Tables, Part 2, Civilian*. H.M.S.O.). This rate was a decrease of 1.1 per 1,000 from the previous year and of 3.2 per 1,000 from 1947, when the rate of 20.5 per 1,000 was the highest since 1921. The rate for 1949 was higher than those for the years 1929–43 inclusive.

Illegitimate live births numbered 36,907. These were 5.1% of the total number of live births and 0.3 below the percentage for 1948. During 1941–5 illegitimate births constituted 6.9% of total live births and reached their peak in 1945, when they were 9.3%. During 1936–40 they constituted 4.2% of total live births.

The stillbirth rate in 1949 was 23 per 1,000 total live births —the same figure as in 1948. These two figures are the lowest recorded since registrations of stillbirths began in the second half of 1927.

The number of male births per 1,000 female births was 1,061, being the same as in the two previous years.

In 1949 marriages numbered 375,041, representing a rate of 17.1 per 1,000 population, compared with 18.2 in 1948 and 18.6 in 1947. There were more men married at the age of 23 than at any other single year of age, and the corresponding age for women was 21.

Of legitimate maternities, 42.2% were to mothers with no surviving previous child, 32.1% to mothers with one surviving child, and 13.7% to mothers with two. Multiple births occurred in 9,328 maternities, of which 87 produced triplets.

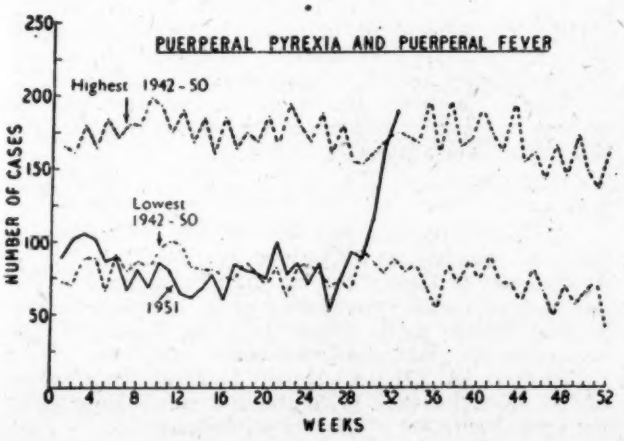
About 59,000 confinements took place within eight and a half months of marriage, and of these about 41,000 were within six and a half months of marriage.

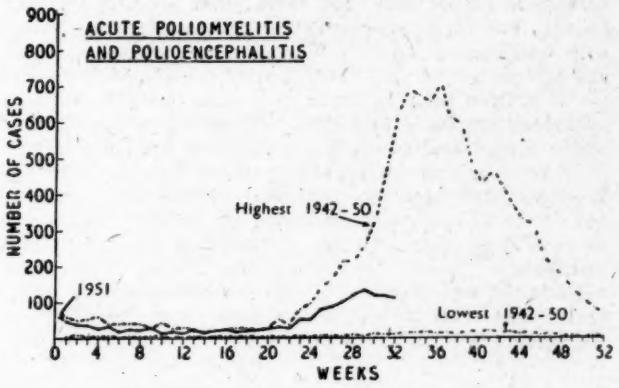
Week Ending August 18

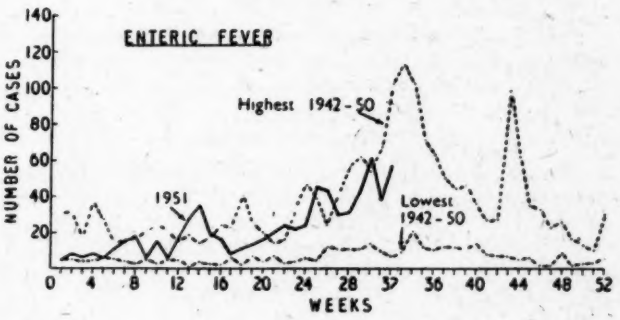
The notifications of infectious diseases in England and Wales during the week included: scarlet fever 477, whooping-cough 3,159, diphtheria 31, measles 3,252, acute pneumonia 233, acute poliomyelitis 120, dysentery 153, paratyphoid fever 52, typhoid fever 10.

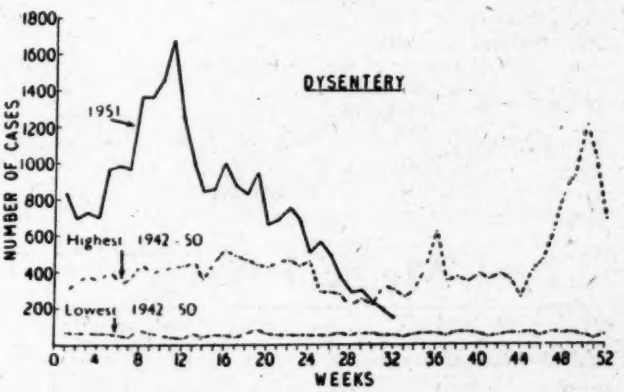
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus -------, the figures for 1951 thus ————. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

In the week ending August 11 the incidences of certain notifiable diseases in England and Wales continued their summer decline. The number of notifications of whooping-cough fell by 244 to 2,661, of measles by 1,323 to 3,621, and of scarlet fever by 178 to 468. Notifications of dysentery numbered 149, 44 fewer than in the previous week. The number of notifications in London fell from 46 in the previous week to 25.

On the other hand, the incidence of typhoid and paratyphoid fever rose. There were 8 more notifications of typhoid fever than in the previous week, making a total of 12, and there were 10 more notifications of paratyphoid fever, making a total of 44. Areas with the greatest local incidence were Liverpool C.B. with 4 cases of typhoid fever notified, and Yorkshire West Riding with 11 notifications of paratyphoid fever.

Meningitis in County Durham

About 70 cases of meningitis of obscure origin have been reported in County Durham, over 60 of them in Boldon U.D. There have been no deaths. The outbreak began six weeks ago and reached its peak about two weeks ago. The occasional case is still occurring. The disease is characterized by a sudden onset with severe headache, vomiting, and photophobia. Sweating, joint pains, stiff

neck, pain in the back, and rapid pulse are also typically found. The cerebrospinal fluid is under increased pressure with lymphocytes up to 220 per c.mm. Chlorides, sugar, and protein are normal. The cause of the disease is thought to be a virus possibly transmitted from mice, and mouse specimens are being examined. However, in many houses where cases have occurred no mice have been found.

There have been no complications, though one man had a relapse after apparent recovery. In one large house 16 out of the 17 occupants contracted the disease. Patients of all ages have been affected, and there is no unusual sex distribution. Some cases have been treated with chloramphenicol, but treatment appears to have made no difference to the course of the disease, which lasts about a week. The incubation period is thought to be about five days.

Poliomyelitis

Poliomyelitis notifications in the week ending August 18 were as follows (figures for last week in parentheses): paralytic, 57 (55); non-paralytic, 63 (57); total, 120 (112).

Poliomyelitis Abroad

Though the incidence of poliomyelitis has shown the usual seasonal increase in most countries in the northern hemisphere, it has not in general been exceptional (W.H.O. *Weekly Epidemiological Record*, August 15). In the U.S.A. 1,203 cases were recorded during the week ending August 4, as compared with 1,185 in 1950 and 2,446 in 1949. Up to July 28 the incidence was lower than last year in France and the German Federal Republic, and lower in Sweden until the end of June.

A heavy outbreak of poliomyelitis is reported from the Saar; 80 cases have been reported, of which 6 were fatal, as well as 47 suspected cases. Increases in incidence have been reported from Austria, Italy (382 cases in June, as compared with 252 last year), the Netherlands, and Switzerland (77 cases during July 1–28, as compared with 58 last year).

Medical News

British Medical Services in Korea

Nearly 1,000 Commonwealth officers and other ranks are serving in Korea in the medical services of the 1st Commonwealth Division. They are the medical personnel of the 26th British, 60th Indian, and Canadian field ambulances attached to the three Commonwealth brigades. Other medical units include a field surgical team with one surgeon, one anaesthetist, and eight other ranks, a field transfusion team (one doctor and three other ranks), and two mobile dental teams each with one officer and three other ranks. Evacuation behind the field ambulance advance dressing station is the responsibility of the United States medical services, which take Commonwealth patients back by air, assisted by the Royal Australian Air Force, to the 29th British General Hospital in Japan. This hospital, which arrived from the United Kingdom at the end of 1950, has now a capacity of 600 beds. Its personnel comprises 24 officers, 229 other ranks, 50 Queen Alexandra's Royal Army Nursing Corps officers, two British Red Cross welfare officers, and includes two surgeons, two physicians, and one or two anaesthetists. There is also in Japan an Australian General Hospital of 200 beds and a Canadian increment of surgeons, nurses, and orderlies. Near the hospital is a convalescent depot staffed by five officers and 52 other ranks for the rehabilitation of troops fit to return to duty. Treatment includes physiotherapy, remedial exercises, graduated physical training, occupational therapy, and welfare and entertainment facilities designed to dispel the hospital atmosphere. Casualties coming home are flown out by the R.A.F. and reach this country in about eight days via Singapore and the Middle East.

History of the R.A.M.C.

Not Least in the Crusade, a little book by Peter Lovegrove, is a good deal more than the story of the work of the Corps since its foundation on June 23, 1898, and the events which led to its creation. There is an interesting brief survey of medical services in the British Army since the time of Richard the Lion Heart's expeditionary force in Palestine (1190), and a number of good illustrations, including a colour plate of the first full-dress uniforms. The book is obtainable from the Editor of the Army Medical Services Magazine, R.A.M.C. Depot and T.E., Queen Elizabeth Barracks, Crookham, Hants, at 1s. 6d. in paper covers (5s. in cloth boards), plus 6d. for postage and packing.

Special Diets for Invalids

The Ministry of Food announces that following the recent increases of the meat ration the special allowance of meat for patients suffering from nephritis with gross oedema and albuminuria or from hypoproteinaemia will now revert to four extra rations a week. Children under 5 years old who suffer from these diseases will continue to receive the same amount of meat as adult patients. The arrangements for extra rations for invalids described in MED.2 (1950) are revised accordingly. Patients who are at present drawing six extra rations a week on their existing authority may continue to do so until that authority expires.

New Members of Medical Research Council

Professor G. L. Brown and Sir James Rögnvald Learmonth have been appointed members of the Medical Research Council from October 1.

Work of King Edward's Hospital Fund for London

The recently issued *Fifty-fourth Annual Report* shows the very valuable work being done by this charitable Trust to supplement the National Health Service, to aid the remaining independent hospitals and institutions, and to improve hospital work through research and teaching. With a capital of between six and seven million pounds, and many private bequests and donations, together with special grants from other bodies such as Lord Nuffield's Trust for the Special Areas, which has so far given a total of £1,350,000, the Fund is in an extremely strong financial position and able to make sizable grants to many hospitals and institutions. Those inside the Health Service receive money to provide amenities for patients and staff (tennis courts, wireless sets, cinema equipment), those remaining independent are helped to build new *x*-ray departments or re-equip their kitchens. A special programme of homes for the aged sick is gradually being realized: the Fund has opened some homes itself, and assisted others, including the Thomas Barlow Home of University College Hospital. Convalescence is another field of development, and a special report was recently issued on the subject. An inquiry is in progress on the present scope for voluntary service in hospital, and also a hospital costing investigation for the Ministry of Health. Schools of hospital administration, hospital catering, and nursing management have been set up, and advisory services are run in some aspects of these subjects. The famous Emergency Bed Service has produced approved schemes to make the best use of the hospital beds available in London during times of epidemic.

Will

Dr. Charles Richard Box left £77,872. After various bequests, including £1,000 to the Worshipful Society of Apothecaries of London, he left the ultimate residue, after the death of certain beneficiaries, to St. Thomas's Hospital Medical School, to be known as "The Box Fund," the income to be used to assist students. Professor George Ernest Gask left £37,264. He left £1,000 to the governors of the medical college of St. Bartholomew's Hospital for the general purposes of the medical college.

COMING EVENTS

New Society for Hospital Biochemists

A meeting to which all hospital biochemists are invited will be held at Preston Royal Infirmary on September 29, at 11 a.m., to discuss the formation of an association. The morning will be devoted to demonstrations, and the proposed association will be considered in the afternoon. The primary aim is to raise the standard of hospital biochemistry. Anyone interested in attending the meeting should write to Mr. E. B. Love, at the department of biochemistry at Preston, before September 15, letting him know whether they can provide a demonstration, and, if so, how much space, etc., will be required, and also whether they wish to have lunch (free) at the infirmary.

Heberden Oration

Professor E. C. Kendall, of the Mayo Clinic, will deliver the Heberden Oration on "The Adrenal Cortex and Rheumatoid Arthritis" at B.M.A. House, Tavistock Square, London, W.C., on Wednesday, September 19, at 5 p.m. All members of the medical profession are invited to attend.

Lectures at Leeds

Dr. J. R. Rees will deliver the inaugural lecture at the Faculty of Medicine of the University of Leeds in the Riley-Smith Hall of the University Union, Leeds, on Tuesday, October 9, at 3 p.m. His subject is "The Sick Man and the Community." On Thursday, October 18, at 3 p.m., Dr. Waltman Walters will deliver the Moynihan Lecture on "Unilateral and Subtotal Adrenalectomy in the Treatment of Hyperfunctioning Lesions of the Suprarenal Cortex" in the Riley-Smith Hall of the University Union. All members of the medical profession are invited to attend the lectures.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday

EDINBURGH POSTGRADUATE BOARD FOR MEDICINE.—At Edinburgh University (Anatomy Lecture Theatre), September 4, 4.30 p.m., *"General and Local Factors Affecting Blood Flow,"* by Professor E. P. Sharpey-Schafer.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Evans.—On August 12, 1951, at Nuffield House, Guy's Hospital, London, S.E., to Winifred, wife of Dr. Michael L. Hudson Evans, a son.

Guthrie.—On August 10, 1951, at Parkgrove Nursing Home, Glasgow, to Olive (formerly Parson), wife of Dr. John Guthrie, a daughter.

Hollman.—On August 26, 1951, at University College Hospital, London, W.C., to Dr. Catharine Hollman (formerly Large), wife of Dr. Arthur Hollman, a daughter.

Howe.—On August 13, 1951, at Bromley, to Eva (formerly Schubert), wife of Marcus S. Howe, *M.C.*, M.R.C.S., L.R.C.P., D.A., a son—Peter Slade.

Martin.—On August 22, 1951, at Morriston Hospital, Swansea, to Sylvia (formerly Gilbert), wife of Dr. Hugh Martin, a son.

Parker.—On August 12, 1951, at Birmingham Maternity Hospital, to Dr. Barbara Parker (formerly Owens) and Bernard Parker, M.R.C.O.G., a son.

Roche.—On August 5, 1951, at St. Teresa's Hospital, Wimbledon, to Susan (formerly Tyrrell), wife of G. K. T. Roche, M.B., B.S., D.A., a son—Stephen John.

Thomson.—On August 15, 1951, at Ashlington Nursing Home, Gosforth, to Dr. and Mrs. Donald Thomson, Stanhope, Co. Durham, a son.

MARRIAGES

Robinson—Harrison.—On August 21, 1951, at Cambridge, James Roper Robinson, M.B., B.Chir., of Emmanuel College, Cambridge, to Marion F. Harrison, of Wellington, New Zealand.

Sudbury—Sadler.—On June 16, 1951, at St. Paul's Presbyterian Church, South Croydon, John Roger Sudbury, M.B., B.Ch., D.Obst.R.C.O.G., to Mary Helen McMorran Sadler.

DEATHS

Boylan.—On August 14, 1951, Peter Boylan, M.B., B.Ch., of 326, Hoe Street, Walthamstow, London, E., aged 55.

Byrd.—On August 10, 1951, at his home, Croft House, Glenridding-on-Ullswater, Penrith, Colin Bostock Byrd, M.R.C.S., L.R.C.P., aged 58.

Evans.—On August 14, 1951, at Westgate, Nottage, Glamorgan, Thomas John Evans, M.B., F.R.C.S.Ed., husband of Mary Evans, M.D. (formerly Kane).

Goldie.—On August 12, 1951, at Winchester, Arthur Evelyn Goldie, M.B., Ch.B., aged 77.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Tuberculous Endometritis and Pregnancy

Q.—*As a result of a diagnostic curettage for menorrhagia, a patient has been diagnosed as suffering from tuberculous endometritis. There is no evidence of tuberculosis elsewhere. She wishes to have a baby. (1) What are her chances of a successful pregnancy? (2) What effect would pregnancy have on her tuberculosis? (3) Is chemotherapy indicated, and, if so, what course of treatment is suggested?*

A.—(1) If the tubes are closed—and there is at least a 50% chance of this in such a case—there is practically no chance of pregnancy even if the infective process is arrested. If the tubes are not irreparably damaged there is a possibility of pregnancy, but it is extremely remote. Chemotherapy, if successful, may well improve the prospects, and at least one case of pregnancy following such treatment has been recorded within the last year. Such treatment, however, is still under trial and it is too early to assess the results.

(2) If conception occurs before the infection is completely eradicated, which is very unlikely, there is probably some risk of it causing a miliary spread of the disease. At least this complication is recorded when an ovum has become implanted in a tuberculous tube.

(3) The place and value of chemotherapy for tuberculous endometritis are at present under investigation, and the time is not ripe for a confident opinion. Chemotherapy is worth trying in such a case, and a suitable course would be streptomycin 0.5 g., twice daily intramuscularly, and *para*-aminosalicylic acid (P.A.S.) 3 g., six times a day by mouth, both being given for 60 to 90 days. Larger doses of P.A.S. (up to 30 g. daily) are sometimes recommended, but most patients cannot tolerate them.

Examination of the Male in a Nullity Suit

Q.—*In a nullity suit I have been asked to "ascertain whether the male is capable of performing the act of generation." What examination should be made, and how should the results be presented to the Court?*

A.—In nullity suits in which it is alleged that the marriage has not been consummated it is usual for two medical inspectors, appointed by a Registrar of the Divorce Division, to examine both husband and wife (if both consent) and to issue a joint report. If the case is contested other medical evidence may be brought by either party. A marriage can be annulled on the grounds of inability of either partner to consummate it, the impediment being irremediable and having been present at the time of marriage but the other partner being unaware of it at that time. Sterility is not grounds for annulment, so in ascertaining "whether the male is capable of performing the act of generation" the medical examiner is concerned with potency and not fertility. He has to decide primarily whether the man can carry out complete coitus.

The male genitalia must be examined for physical defect, and special attention paid to evidence of nervous, endocrinous, or other general diseases which might cause impotence. Impotence, however, is more often of psychological origin, associated sometimes with matters of upbringing and environment. The man has therefore to be questioned very carefully about his sex life, the practice of masturbation, his outlook on women and marriage, and the frequency of erection, etc., for any possible guide to assist in the assessment of his potency. This aspect of the case bristles with difficulties, for the examiner is largely dependent on unconfirmed statements by the man. Moreover, a man may have

successful intercourse with one woman but prove impotent with another. If the wife is also available for questioning and examination it is sometimes easier to reach a conclusion.

In most cases where the man is physically normal it is wise for the medical examiner to state only that he is unable to find any physical bar to the consummation of the marriage. He may feel disposed to mention any significant points in the history which may indicate or refute psychological impotence, but when a conclusion about the marriage being consummated depends on weighing the counter-statements of the two parties, rather than on signs to be elicited by medical examination, it becomes a matter for the Court.

When examination reveals some physical defect which prevents coitus the medical witness is expected to give an opinion on whether it can be corrected by operation or other forms of treatment.

Low Blood Pressure in Pregnancy

Q.—*What is the significance of a low maternal blood pressure in pregnancy (100/60)? Is there any increased likelihood of miscarriage or foetal abnormality associated with such a finding? Is any treatment indicated?*

A.—A blood pressure of this level is usually of no significance, especially during the middle trimester of pregnancy, when the pressure normally falls. However, anaemia or other general disease should be excluded. The old idea that hypotension in late pregnancy is associated with uterine inertia in labour is no longer accepted, and there is no relation between the level of the blood pressure and the occurrence of foetal malformations.

No treatment is indicated unless the symptoms and signs of disease are present.

Lateness in Learning to Speak

Q.—*A boy aged 2½ years can speak only a few words, such as "Mummy" and "Daddy," and these are said in a sing-song voice. He first began to use these words at the age of six months. In every other respect he appears normal. What is the likely explanation of this failure to develop his speech, and what treatment is advised?*

A.—Lateness in speaking often runs in families, and this factor should be investigated. High-tone deafness is a very important cause of lateness in speaking, and it should be looked for in this boy, especially in view of the "sing-song" voice. Mental retardation, one of the commonest causes, must be excluded. Delay in the establishment of handedness is an occasional cause of lateness in speaking, and there are certain rare psychological causes. Obviously treatment cannot be prescribed before a diagnosis is made. The boy should be examined by an experienced E.N.T. specialist for high-tone deafness, and, if nothing is found, by a paediatrician experienced in developmental diagnosis.

E.S.R. in Rheumatic Chorea

Q.—*Is the erythrocyte sedimentation rate always raised in rheumatic chorea whether or not there is an associated rheumatic carditis?*

A.—The sedimentation rate is usually normal in rheumatic chorea in the absence of other signs of rheumatic activity such as carditis, arthritis, fever, and rash. This applies both to rheumatic chorea starting as such and to the chorea which may follow an attack of rheumatic fever. The latter type of case may show nodules with a normal sedimentation rate.

Desensitization to Sera

Q.—*What is the best way of desensitizing persons who are sensitive to sera? What are the risks?*

A.—Hypersensitivity to foreign protein such as is acquired following the injection of antisera prepared in the horse does not usually persist for more than 6 to 12 months. The degree of reaction from a second injection given within this period will vary with the amount and nature of the original antiserum. The larger the dose and the cruder the antiserum the greater will be the risk of a hypersensitive reaction from the second injection. However, this reaction can be prevented or controlled in most cases by the hypodermic injection of 0.5 to 1 ml. of 1 in 1,000 adrenaline. If hypersensitivity to foreign protein is known to be more persistent in any patient, as shown by a marked weal and erythema reaction when a small dose—e.g., 0.1 ml. of 1 in 1,000 dilution—of the test antiserum is injected intradermally, it is doubtful if the patient can then be satisfactorily desensitized. Probably the best procedure in these circumstances is to give a small dose, say 0.1 ml., of the serum diluted 1 in 10 subcutaneously, and if there is no reaction within half an hour to proceed with the larger dose, giving it very slowly intramuscularly (not intravenously), and having an adrenaline syringe charged ready for use in case there should be any signs of distress.

Contraception with Oestrogens

Q.—*In a Refresher Course article on "Menstrual Disorders and the Menopause" it is stated that stilboestrol will almost always inhibit ovulation (Journal, 1950, 2, 1269). Why is this aesthetic method never advised for contraception?*

A.—Because there are other simpler and more reliable methods of contraception. In order to be certain of preventing ovulation oestrogens need to be administered within five days of the onset of the period in adequate doses to lead to a non-ovulatory withdrawal bleeding. This demands intelligent study on the part of the patient, considerably greater than is required for the successful use of orthodox contraceptive measures. Furthermore, there are risks, such as the development of fibro-adenosis of the breasts, which contraindicate prolonged oestrogen therapy. It may be justifiable to accept these risks as an alternative, say, to incapacitating dysmenorrhoea, but it is hardly justifiable to use oestrogens permanently as a contraceptive.

NOTES AND COMMENTS

Sensitivity to Local Penicillin.—Dr. HAROLD WILSON and Dr. F. RAY BETTLEY (London) write: A correspondent writing ("Any Questions?" July 28, p. 250) to ask whether sensitivity to local penicillin necessarily implied sensitivity to parenteral administration was answered with a simple affirmative. Once the epidermis has become sensitized there is an increased liability to a reaction from penicillin injections, but it is an incorrect assumption that the one *invariably* follows the other. The patch test has, for example, been found of doubtful value as an index to general penicillin allergy (Peck *et al.*, *J. Amer. med. Ass.*, 1948, **138**, 631; Haswell and Wilkinson, *Lancet*, 1946, **1**, 308). The intramuscular injection of penicillin into four patients who had recently recovered from a proved penicillin dermatitis did not provoke a single reaction (Marsh and New, *Nav. med. Bull., Wash.*, 1948, **48**, 391). Further, this aspect of the problem of penicillin allergy was the subject of prolonged study by Weiss, whose experiments led him to conclude that epidermal sensitivity was not always accompanied by vascular sensitivity; it might occur, but did not do so often (Weiss, R., *Arch. Derm. Syph., Chicago*, 1947, **56**, 333). While, therefore, the presence of epidermal sensitivity indicates a need for caution, the injection of penicillin should not be unconditionally withheld, particularly when there are urgent indications for its use.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.
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